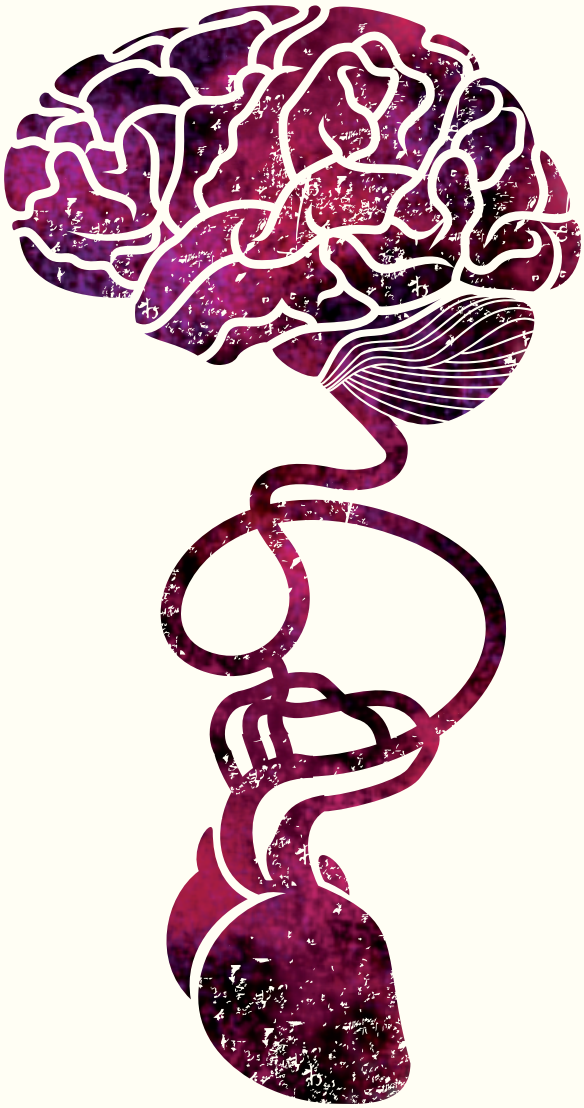

Cost-effectiveness modelling of complex diagnostic strategies in cardiovascular diseases; early HTA supporting healthcare decision making

Anne-Claire M.M. Peultier

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Cost-effectiveness Modelling of Complex Diagnostic Strategies in Cardiovascular Diseases; early HTA supporting healthcare decision making

Modellering van kosten-effectiviteit van complexe diagnostische strategieën bij cardiovasculaire aandoeningen; vroege HTA ter ondersteuning van beslissingen in de gezondheidszorg

Thesis

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1

Introduction

1.1 PRINCIPLES OF HEALTH TECHNOLOGY ASSESSMENT

Along the evolution of methods in social and applied sciences such as clinical epidemiology and health economics, Health Technology Assessment (HTA) has become, over the last few decades, an internationally active field supporting policy decisions in healthcare. HTA is defined as ''the systematic evaluation of the properties and effects of a health technology, addressing the direct and intended effects of this technology, as well as its indirect and unintended consequences, and aimed mainly at informing decision making regarding health technologies'' [1]. In a context of wide expansion and diffusion of medical science and technologies leading to increased healthcare costs, HTA has been increasingly used to inform a fair decision-making process regarding the financing or reimbursement of medical technologies [2,3,4]. HTA is used to inform health care policy on how to allocate scarce resources in the most efficient way in a context of constrained optimisation. Health technologies include diagnostic technologies, vaccines, pharmaceutical drugs, devices, medical and surgical procedures. Mass media campaigns or comprehensive healthcare strategies might also be assessed.

HTA is conducted by interdisciplinary groups that use frameworks drawing on different methods [1]. Economic evaluations constitute the core of HTA and provide insight into the costs and effects of a new technology compared with another one [5]. They are defined as ''the comparative analysis of alternative courses of action in terms of both their costs and consequences'' [5]. For example, the comparative effectiveness of a new diagnostic imaging tool can be assessed and balanced against the costs of an alternative diagnostic approach, such as current care or watchful waiting. As such, the incremental concept is a key component of the decision-making process that is captured by the incremental cost-effectiveness ratio (ICER). The ICER is the average cost that needs to be invested per patient to gain an additional unit of health when using the new technology compared to the existing one. Therefore, considering all relevant comparators against which to assess the value of a new technology is crucial [6]. Framing is an essential first step of an economic evaluation, during which the comparator but also the patient population, the indication, the decision-maker, the perspective and the outcomes are chosen. Cost-effectiveness analysis (CEA), and cost-utility analysis (CUA) more generally speaking, use the quality-adjusted life-year (QALY) as a generic measure of effect or health gain. The QALY combines the length of life in years with the quality of life spent during these years [5].

Economic evaluations usually require drawing on evidence from various sources. Economic evaluations relying on empirical data from experimental or observational studies

have various limitations. To overcome these limitations, decision analytic modelling (which falls under economic evaluations) involves the application of mathematical techniques to synthesise and bridge existing data and information from multiple sources concerning healthcare processes and their implications [5,7]. A key purpose of decision modelling in healthcare is to provide a framework for decision-making under the conditions of uncertainty [6]. The key concepts of uncertainty that shape the exercise of decision modelling include variability across patients, parameter uncertainty, decision uncertainty and patient heterogeneity [6]. Variability refers to the inevitable difference in clinical events and health-related quality of life experienced by patients [6]. Parameter uncertainty relates to the precision of an input estimate (probability of a clinical event or cost) and can be addressed with stochastics (random probability distribution) or non-stochastic (bootstrapping) statistical methods. Decision uncertainty relates to the cumulative effect of the uncertainty around all parameters. Patient heterogeneity relates to the uncertainty driven by the patient's characteristics such as age, gender or individual risk factor. In addition to these, the model structure itself, by its design and the structural assumptions it relies on, is a source of uncertainty. The inclusion of a relevant comparator (often current care), the inclusion of relevant events (in a decision tree, for example), the use of alternative statistical methods and the clinical uncertainty were identified as four categories of structural uncertainty [8]. Dealing with uncertainty is particularly relevant when CEAs are performed in the early stages of development of a new medical technology.

Early-CEAs are used to inform industry and other relevant stakeholders about the potential value of a new technology alongside the research and development process [9]. The goal of early-CEAs is to mitigate the risks perceived by the stakeholders and increase the chances for market access and reimbursement [9]. Early-CEAs may help the manufacturer in identifying and selecting high value development strategies that provide substantial returns on investments as well as patient and societal value at an early stage [10]. Diagnostic technologies are characterised by specificities that make their early-CEA particularly relevant and efficient [11]. These specificities include lower barriers to development and market entry and increased number of potential uses or indications, compared with therapeutics, as well as an increasing range of new diagnostics being developed [11]. These facts, combined with the rapidly increasing costs of advanced diagnostic technologies, support an earlier and iterative approach to economic evaluations of diagnostics along the development phase [11]. This early approach can be key in improving the efficiency of the innovation process of diagnostics [11]. Early assessment of an imaging tests may encourage developers to improve the technical features (resolution, sensitivity or specificity for example) that will provide the highest societal value.

In various countries worldwide, reimbursement decision-making by the payer (mostly government agencies) requires the submission of a value dossier by the manufacturer. Values dossiers cover a variety of topics and methods in which HTA plays a prominent role in gathering clinical and economic evidence. These dossiers are subject to assessment that can lead to a positive or negative reimbursement decision. A negative recommendation may have serious consequences in terms of market access and diffusion of the technology. Reimbursement decision-making remains the sole responsibility of each country and variations in the use of HTA practices have led to differences in reimbursement recommendations and decisions across European jurisdictions [12,13,14]. In the United States (US), HTA is used in a more indirect way ''in the background'', by clinical guidelines writers for example. The resistance to economic evidence in the US mostly found its roots in both a lack of understanding and training about resource constraints and tradeoffs and a lack of trust in the methods of CEAs [15,16].

In a context of an increasing number of medical technologies developed and sometimes fast evolving care, transferring health economic evidence from a country to another one might be a fast and efficient method to inform decision makers in various jurisdictions. Economic evaluations are considered to be generalisable when their results can be applied without additional adaptation to other countries [17]. In contrast, they are considered transferable when adaptations (adjustments based on local parameters) are necessary [17]. Various critical factors might hinder the transferability of economic evaluations [18]. The value of a health technology is highly dependent on the context in which it will be used. For example, an imaging test that is cost-effective in the United Kingdom (UK) might provide bad value for money in Hungary or the US. Similarly, an imaging test that is cost-effective for a population of patients at the country level might be an investment that is not cost-effective at the hospital level.

As mentioned before, diagnostic technologies are characterised by specificities that might affect their reimbursement by health authorities. First, diagnostic tests are often reimbursed either as part of a medical package for a disease, as part of a diagnosis-related group (DRG) or based on a fee-for-service, contrary to therapeutics that are reimbursed for a specific indication. Second, a diagnostic test provides only information and this fact implies that its efficacy is indirect. More precisely, a test can have an impact on patients only via specific actions such as a change in medication or the decision to perform a surgery. Therefore, the health economic value of a test depends on whether or not these actions will lead to a health gain at an overall acceptable cost. The hierarchical model of efficacy by Fryback and Thornbury illustrates that even the highest technical efficacy (resolution) or the highest accuracy (sensitivity, specificity) of an imaging test may not necessarily guarantee patient outcome efficacy or societal efficacy

[19]. Third, tests have different purposes, and therefore different applications, along the progression of a single disease. These purposes range from risk factor screening, disease screening, diagnosing, prognosing, testing for the choice of therapy, testing to monitor the response of a therapy and testing for surveillance [20]. For these reasons, it is crucial to define the ultimate goal of a test for the patient, in terms of biological outcomes, risk reduction of clinical events (like stroke or myocardial infarction) or improvement in length and/or quality of life. Altogether, these specificities make the health economic assessment of diagnostic tests more challenging compared to drugs, and the framing of the study crucial. These specificities also imply that the evaluation of the long-term impact of diagnostics requires a combination of data from clinical research and disease and population modelling.

1.2 CARDIOVASCULAR DISEASES

Cardiovascular diseases (CVD) are a group of disorders of the heart and blood vessels [21]. Among others, they include coronary heart diseases (diseases of the blood vessels supplying the heart muscle) and cerebrovascular diseases (diseases of the blood vessels supplying the brain) [21]. Atherosclerosis, which is characterised by the deposition of fatty materials on the inner wall of arteries, and its complications, are responsible for the large majority of all cases of CVD. Globally, CVD are the number one cause of death [21]. By 2030, 23.6 million people are projected to die from CVD, mainly from heart diseases and stroke [21]. In addition to the high morbidity, CVD lead to a high economic burden worldwide [22,23]. This thesis focuses on two CVD disorders: stroke (and specifically ischaemic stroke) and two subcategories of coronary artery disease (CAD) (acute coronary syndrome (ACS) and non-obstructive coronary artery disease (NOCAD)).

1.2.1 Stroke

Definition of the disease and epidemiology

Stroke is defined by the World Health Organization as a "a clinical syndrome typified by rapidly developing signs of focal or global disturbance of cerebral functions, lasting more than 24 hours or leading to death, with no apparent causes other than of vascular origin" [24]. Globally, about 80% of strokes are caused by ischaemia, which is an interruption of the blood supply, usually caused by a blood clot, while the remaining 20% is due to haemorrhage, which is characterised by a rupture of a blood vessel or an abnormal vascular structure [25]. These proportions vary across populations.

Given their different cause, ischaemic and haemorrhagic strokes require different therapeutic strategies.

In 2016, stroke was the second largest cause of death globally, with 13.7 million people experiencing an incident stroke and 5.5 million people dying from it [26]. Furthermore, important geographical variations have been observed worldwide from 1990 to 2016: the largest increase in stroke incidence was observed in East Asia and the largest decrease in southern Latin America [26]. The incidence of stroke increases significantly with age. Finally, stroke incidence amongst those aged 55-75 years is significantly greater for men than for women [26].

Humanistic and economic burden of disease

Stroke is the second leading cause of death and a major contributor of disability in the world [26]. Although mortality rates have decreased sharply from 1990 to 2016, the decrease in incidence has been less important, which suggests that the burden of stroke is inclined to remain high [26]. Considering the demographic transitions of populations in the developing countries and the ageing of the world population, the worldwide burden is even likely to increase [27]. Prevention of stroke in people aged 75 years and above is expected to play a major role in relieving the future global burden. Many stroke survivors are chronically disabled or functionally dependent and suffer from severe health loss.

Stroke is a huge public health burden with consequences such as increased healthcare utilisation, decreased productivity (resulting from morbidity and mortality) or the need for informal care, which result in substantial personal and societal costs. As such, costs are divided into direct healthcare costs (transport, hospitalisation and acute care, medication, rehabilitation, physician consultations, nursing care, long-term care facilities), and indirect costs (lost productivity, informal care).

Impact of stroke on quality of life and life expectancy

The impact of stroke on the patients' quality of life depends on the severity of the stroke, which determines the degree of disability or dependence in daily life. Survivors of a stroke can experience a wide range of physical and cognitive impairments that include language and communication disorders (aphasia), limb weakness causing difficulties in walking and balancing, visual impairment, fatigue, difficulties in swallowing leading to a higher risk of pneumonia, loss of bladder and bowel control, anxiety or depression [28-33]. These effects can have a huge impact on social integration. Various studies have measured the quality of life of stroke survivors, based on the severity of the stroke. For example, based on a literature review, utility values assigned by stroke survivors ranged

from 0.72 after a minor stroke to 0.41 after a major stroke [34]. Furthermore, dependent patients experience an increased mortality compared to independent patients, who themselves experience an increased mortality compared to the general population [35,36].

Diagnosis and diagnostic imaging of acute ischaemic stroke

Acute patients presenting with stroke-like symptoms need to receive a timely assessment of the nature and extent of brain damage before clinicians can decide on the type of acute treatment. In this context, the role of diagnostic neuroimaging has become pivotal. A variety of imaging techniques are available to reliably identify a stroke, determine the stroke type, assess the eligibility of treatment options and predict the outcomes [37]. Differential diagnosis aims at distinguishing an ischaemic stroke from a haemorrhage one or other causes and is reliably determined using unenhanced computed tomography (CT) imaging or magnetic resonance imaging (MRI). Once a haemorrhage has been ruled out, the selection of patients with ischaemic stroke for treatment requires crucial additional imaging information related to stroke infarct core, ischaemic penumbra or degree of collaterals, vessel occlusion and thrombus location [37]. In addition to common modalities (CT, CT angiography (CTA) and MRI), advanced imaging modalities such as perfusion CT and MR angiography (MRA) provide relevant and accurate information [37]. The diagnostic workup of the patient with ischaemic stroke is based on a combination of these imaging modalities (CT + CTA + CTP, for example). This combination varies based on the availability of the imaging techniques and on the patient's prior eligibility to treatments delivered in the healthcare facility. Over the past years, the need for this advanced imaging information has been created and intensified by the rapid evolution of treatments for ischaemic strokes.

Acute ischaemic stroke treatments

The effectiveness of acute ischaemic stroke treatments is time dependent. Under certain patient eligibility criteria, acute ischaemic strokes can be treated by an intravenous recombinant tissue plasminogen activator (tPA) which dissolves the blood clot and restores the blood flow in the brain. Intravenous tPA has been proven most effective and recommended within 4.5 hours from stroke onset [38-40]. Recent evidence has showed the efficacy of tPA until 9 hours after stroke onset [41,42]. In addition, intra-arterial mechanical thrombectomy (MT), which consists of the surgical removal of the blood clot with a stent retriever, has become, over the last decade, the cornerstone of acute ischaemic stroke management in patients with a large vessel occlusion. Multiple randomised trials have confirmed the efficacy of this treatment within 6, 8 and 12 hours from stroke onset in case of a large occlusion [43]. Recent evidence demonstrated its efficacy from 6 hours until 16 and 24 hours from stroke onset in eligible patients [44,45].

Patients with acute ischaemic stroke and large vessel occlusion are eligible to the late-window (6 to 24 hours) MT based on strict advanced imaging criteria [44,45]. Evidence suggests that patients who do not meet these criteria do not benefit from MT. Finally, MT and tPA can be administered alone or in combination with each other.

Potential value of new imaging test

In the current context of ischaemic stroke care, which relies on a comprehensive and relatively expensive imaging workup, new emerging and innovative technologies such as dual energy CT and, more recently, spectral photon-counting CT (SPCCT) could add value. Currently being developed with the goal to be a widely accessible technology, SPCCT is expected to improve acute stroke treatment decision-making by better quantification of brain perfusion impairment [46,47]. This improved quantification would be eased by a higher spatial resolution and, in turn, better characterisation of brain tissues [48]. These technical improvements would allow more accurate identification of stroke patients who would benefit from late MT, exclude patients who will not benefit from treatments, and, as such, ensure an optimised use of healthcare resources and maximise patient health outcomes. Furthermore, SPCCT, by substituting the comprehensive imaging diagnostic workup of ischaemic stroke patients with a single imaging test could decrease the current diagnostic time and therefore contribute to increasing patient health outcomes. Finally, by allowing a diagnosis based on a single test, SPCCT could simplify the logistical organisation, be less expensive than the current imaging workup, more widely affordable to hospitals and contribute to increased patient access to acute ischaemic stroke care.

1.2.2 Coronary artery disease, acute coronary syndrome and non-obstructive coronary artery disease

Definition of the disease and epidemiology

CAD usually is characterised by the progressive narrowing of the coronary arteries by atherosclerosis, which is the buildup of fatty deposits or plaques. Plaques and plaque rupture or erosion can cause vessel occlusion and lead to cardiovascular events, such as MI, stroke and/or death). ACS is a subcategory of CAD that refers to a range of conditions where the blood supplied to the heart muscle is suddenly blocked or significantly reduced, which can lead to the death of cells in the heart tissues. Patients with ACS almost always present with severe chest pain or discomfort which are the leading symptoms initiating the diagnosis and require immediate referral to the emergency ward [49]. ACS includes myocardial infarction (MI) and unstable angina that differ by their physiopathology and treatment [49,50]. Non-obstructive CAD (NOCAD) is another subcategory of CAD in which the atherosclerotic plaques do not obstruct the blood flow [51]. Patients

with NOCAD can be symptomatic or asymptomatic but they experience a higher average risk of major adverse cardiovascular events (such as MI and stroke), compared with individuals with no apparent CAD [51,52].

Although the incidence has decreased over time in developed countries, CAD remains a major cause of death and disability in these countries [53,54]. In low- and middle-income countries, CAD is the leading cause of death in adults [54,55]. While women were historically at a lower risk of CAD, they have been experiencing an increase in cardiac events such as MI [54,56]. The incidence of coronary events increases with age in both sexes.

Humanistic and economic burden of disease

Based on 2016 estimates, the worldwide prevalence of CAD accounted for 32.7% of the global burden of cardiovascular diseases and 2.2% of the global burden of diseases [57,58]. Furthermore, coronary heart diseases were reported to be the cause of death in 19% of men and 20% of women in Europe [59]. The clinical consequences of CAD include major adverse cardiovascular events, such as death, MI and stroke, but also heart failure [58]. A significant proportion of the patients experiencing an MI dies before they reach the hospital or during hospitalisation [60,61].

The largest contributors to the total costs of cardiovascular events are hospital stay and revascularisation procedures, such as cardiac surgery or interventions [58,62,63]. The medication costs for primary and secondary prevention of CAD also contribute to the disease's economic burden [62]. Finally, the indirect costs related to productivity loss due to morbidity and mortality are considerable [58,59].

Impact on quality of life and life expectancy

CAD can lead to hospitalisation and disability and can potentially impact the daily activities of patients [58]. Evidence has shown that survivors of an ACS experience a lower quality of life compared with the general population [64,65]. Marked impairments were found in the dimensions of pain or discomfort, usual activities, depression and fatigue [64,65]. MI specifically remains a feared diagnosis for patients. Following an ACS, the quality of life rises as time passes [66]. Based on the literature, a patient surviving a MI would have a utility of 0.67 during the 12 months post-event and could regain a utility of 0.82 after the first year [67]. Patients with NOCAD can be asymptomatic or experience on-going or episodes of chest pain, which can affect their quality of life. CAD, including NOCAD, is associated with an increased mortality compared to the general population [68,69].

Current care in ACS

Patients diagnosed with an ACS by electrocardiogram and blood tests undergo imaging investigation(s) so that clinicians can personalise the acute treatment. While invasive coronary angiography or coronary CT angiography (CCTA) reveal narrowed or blocked coronary arteries, echocardiogram shows whether the heart is pumping correctly and myocardial perfusion imaging shows the blood flow reduction through the heart muscle. Together with imaging, stress test play an important role in showing how well the heart works under exercise.

The treatment of ACS depends on the clinical type that is diagnosed. Various medications for emergency ACS care may be prescribed, with different goals such as dissolving the clot, improving blood flow or slowing the heart rate, for example. Surgery and other procedures might be needed to restore the blood flow to the heart muscles. These procedures include, among others, percutaneous coronary intervention (PCI) or a coronary artery bypass graft (CABG). PCI, also known as angioplasty with a stent, is a non-surgical endovascular procedure during which a stent is used to open up the part of the blood vessel narrowed by plaque build-up and restore the blood flow. In contrast, CABG is an invasive surgery which diverts the blood around the narrowed part of an artery by creating a new route with a graft from another part of the patient's body. Evidence suggests differences and ACS care within Europe [70].

Current care in NOCAD

The diagnosis of NOCAD is currently based on clinical presentation (chest pain) and imaging. CCTA is usually used to establish the degree of coronary artery plaque-related stenosis; NOCAD refers to a degree of stenosis below the commonly accepted threshold of 50% [71]. CCTA provides limited information regarding the vulnerability of plaques to rupture and the risk of subsequent cardiovascular events [72]. The long-term treatment goals for patients with NOCAD are to relieve symptoms, if any, and lower the risk of cardiovascular events that are caused by plaque rupture. Although medical treatment may stabilise plaques, the residual risks and mechanisms of plaque rupture are unclear. Therefore, the treatment presents great challenges and the optimal therapy per patient is yet to be determined [71]. Medical therapeutic recommendations include a variety of options, including statins, with different levels of evidence regarding their effects [71]. Lifestyle changes are known to play an important role here.

Potential value of new imaging test

In order to reduce the risk of an ACS and CVD in general, unstable atherosclerosis (i.e. plaques at high risk of rupture) has to be detected at an early stage of its development.

Current treatment strategies (medication, PCI and surgical approaches) rely on the quantification of the plaque-related stenosis. This quantification is impaired by the presence of plaque calcification and the spatial resolution of current imaging technologies. SPCCT, by its higher sensitivity to calcification and increased spatial resolution, is expected to improve the accuracy of stenosis measurement. This would reduce the number of unnecessary referrals of a large proportion of patients with CAD to invasive procedures. In addition to stenosis quantification, the improved spatial resolution of SPCCT and its novel image reconstruction algorithms could enable an enhanced characterisation (structure and biology) of atherosclerotic plaques, compared with the currently available imaging techniques. A prototype of SPCCT has shown the ability to differentiate plaque features and components (such as lipid, calcium or fibrosis) [73]. These advances in the analysis of plaque components are expected to allow a better identification of plaques that are at risk of rupture and the implementation of preventive treatment strategies for patients with CAD. These prospects would be particularly valuable in NOCAD which poses a diagnostic challenge.

1.3 Objectives and research questions

The overall objective of this thesis is to assess the potential cost-effectiveness of a currently developed advanced diagnostic imaging technology (SPCCT), to support healthcare decision making in cardiovascular diseases, taking into account international variation. Four research questions are covered:

1) What is known about current care and its variation in four European countries regarding the diagnostic workup and therapeutic interventions for patients presenting with a suspected stroke and patients presenting with ACS?
2) Is SPCCT cost-effective in patients with ischaemic stroke in the UK and the US?
3) Is there international variation in the cost-effectiveness of SPCCT for patients with ischaemic stroke in Europe and is the transfer of an economic model a valid method to obtain country-specific estimates?
4) What is the cost-effectiveness of SPCCT in patients with NOCAD in the UK?

1.4 Outline

Chapter 2 provides a description of stroke imaging and an overview of practice variation across four European countries (Hungary, Germany, Sweden and the UK) based on a systematic literature review. In Chapter 3, we described the patterns of stroke imaging and acute revascularisation therapy and examined variations across European countries based on a clinician survey. In Chapter 4, we used modelling methods to investigate the potential cost-effectiveness of advanced imaging* and MT beyond 6 hours from stroke onset, compared to conventional imaging and standard medical care in the UK. In Chapter 5, we performed model-based CEAs of MT in the extended time window from

stroke onset following advanced imaging*, compared with standard medical care, for 29 subgroups of ischaemic patients in the US. In Chapter 6, we explored the validity of the process of transferring an economic model developed for the UK to Hungary, Germany and Sweden and compared the country-specific cost-effectiveness estimates. In Chapter 7, we examined the diagnostic and treatment strategies for suspected or confirmed ACS, based on a clinician survey, and identified variations in responses across European countries and regions. Chapter 8 provides a model-based CEA of SPCCT versus CCTA in selecting patients with NOCAD who would benefit from statin therapy. Finally, in Chapter 9, we summarise and discuss the results of all the chapters and highlight further research challenges.

* In Chapters 4, 5 and 6, advanced imaging was used as a generic term for publications and should be interpreted as SPCCT within the context of this thesis.

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2

What are the images used to diagnose and assess suspected strokes? A systematic literature review of care in four European countries

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Abstract

Introduction

The cost-effectiveness of clinical interventions is often assessed using current care as comparator. However, evidence suggests practice variation in stroke imaging across countries. For the purpose of feeding into cost-effectiveness analysis, this research aims to describe the patterns of stroke imaging, examine practice variations across countries and, as such, obtain results reflecting current care.

Areas covered

A systematic literature review was conducted to identify original studies reporting the imaging workup used in acute stroke care in clinical practice in Hungary, Germany, Sweden and the UK. Information regarding the type and frequency of stroke imaging was analysed. Computed Tomography (CT) was reported as the main diagnostic imaging modality used in stroke care (78–98% across patient profiles and time periods). This review revealed patterns that were not observed in individual studies. Comparisons of UK studies revealed considerable variations in the proportion of scanned patients and timing of imaging.

Expert commentary

While the evidence about thrombectomy is difficult to translate in clinical practice, the evidence regarding the optimal imaging approach to diagnose stroke patients is lacking. The heterogeneity in stroke imaging reinforces the need to compare the quality of stroke care within and between countries.

2.1 INTRODUCTION

The rapid evolution of stroke treatment over the past years has been geared toward thrombolysis and more recently thrombectomy. Patients presenting with stroke-like symptoms in the hospital require a quick assessment of brain damage and perfusion impairment, making the use of neuroimaging essential. Besides common modalities such as computed tomography (CT), CT angiography (CTA), and magnetic resonance Imaging (MRI), advanced imaging techniques such as perfusion-computed tomography (CTP) and magnetic resonance angiography (MRA) are available and able to provide relevant information during the diagnostic workup in stroke care. Among the new emerging technologies, dual energy CT, and more recently, spectral photon-counting CT (SPCCT) are innovative imaging tools expected to improve stroke treatment decision-making in emergency settings by better quantification of brain perfusion impairment [1]. However, the potential added value of these new techniques in acute stroke care is currently unknown and can only be determined by comparison with the modalities used in current clinical care.

In the management of complex diseases, such as stroke, diagnostic imaging tests influence outcomes indirectly by determining the treatment choice and clinical decision-making [2]. Thus, the relation between the use of an imaging test and the health outcomes is uncertain, making cost-effectiveness evaluations of diagnostic tests sometimes difficult [3]. A crucial first step in assessing the potential value of an imaging technology is to understand the specific clinical context and the current level of provision of competing technologies used in clinical practice: Who and how do we image? Why do we image? For these reasons, assessing the relative value of new technologies such as SPCCT, both in terms of patient outcome and costs, requires an exact understanding of the current imaging practice in acute stroke care. Clinical guidelines are often assumed to represent current practice and used as a proxy in cost-effectiveness evaluations. The European Stroke Organisation (ESO) guidelines for the management of ischemic stroke recommend that patients with suspected transient ischemic attack (TIA) or stroke receive urgent axial brain imaging (cranial CT or MRI). Urgent vascular imaging, such as ultrasound, CTA or MRA, is recommended for patients with a TIA or minor stroke [4].

The assumption that current care is aligned on guidelines is inappropriate when clinical practice substantially differs from guidelines and problematic when clinical practice differs between hospitals or countries. Evidence suggests differences in stroke care [5] and outcomes [6–9] within European countries. The scarcity of and the need for international comparisons and databases have been pointed out by different authors [6–8], suggesting that variations in care need to be understood better. In this context, we conducted

a systematic literature review to identify studies informing of the diagnostic patterns in acute stroke imaging and to examine variations between countries.

2.2 METHOD

2.2.1 Search strategy

A de novo search strategy for finding relevant papers was designed by the researcher (ACP) together with the biomedical information specialist of the medical library of Erasmus Medical Centre of Rotterdam, The Netherlands. The search strategy can be found in the supplemental material number 1. The following databases were researched on the 18 August 2016: Embase, Medline, Web of Science, the Cochrane Library and Google Scholar. All records retrieved from the databases were merged into one database and duplicates were removed. The remaining studies were screened by title and abstract by two independent reviewers (ACP and either KR or JLS) and ineligible publications were excluded based on predefined criteria (described below). The results of both reviewers were compared and any discrepancies were discussed and resolved by consensus. After title/abstract selection, all remaining publications were read in their entirety to determine which ones met all inclusion and exclusion criteria (ACP).

2.2.2 Inclusion and exclusion criteria

Non-English-language publications were excluded, as were conference abstracts, editorials, letters, reviews and books. Articles published before 2008 were also excluded since that was the year in which the latest ESO guidelines for the management of ischemic stroke were published. Non-observational studies such as pilot studies, experimental studies, and RCTs (randomized controlled trials) which did not include an arm focusing on current care were excluded.

Because we were interested in examining a range of healthcare systems, articles were eligible for inclusion only if they reported information on the diagnosis pattern of suspected stroke patients in the real-life practice of all types of hospitals (university, non-university, specialized, community, county) or clinics of Germany, Hungary, Sweden or the UK. Whereas Sweden is known for its early adoption of medical technologies, Hungary tends to be a late adopter. Besides, the UK is of major interest for its publicly funded system while Germany is characterized by its decentralized healthcare organization in which private practitioners play a relatively important role.

The therapeutic scope of the selected studies included ischemic or hemorrhagic stroke, TIA, cerebellar infarction, intracerebral hemorrhage or subarachnoid hemorrhage. Stud-

ies based on a patient population were included only if the sample contained more than an arbitrary cut off of 100 patients. Articles using data collected before and after 2008 were only included if the results after 2008 could be separated from the previous years.

2.2.3 Data extraction

One reviewer extracted the main characteristics from the included studies: first author's name, year of publication, country, clinical setting, study population, study design, origin of data, data collection period and the study goal.

Data extracted with the aim of describing and analysing the state of care included timing indicators related to the process of stroke care and information on the imaging techniques used. Whenever the data was available, the proportion of patients benefiting from each technology was reported. Extracted data were then analyzed and aggregated in a qualitative and quantitative synthesis. The extraction, calculation and reporting method is detailed in the supplementary material 2.

2.3 RESULTS

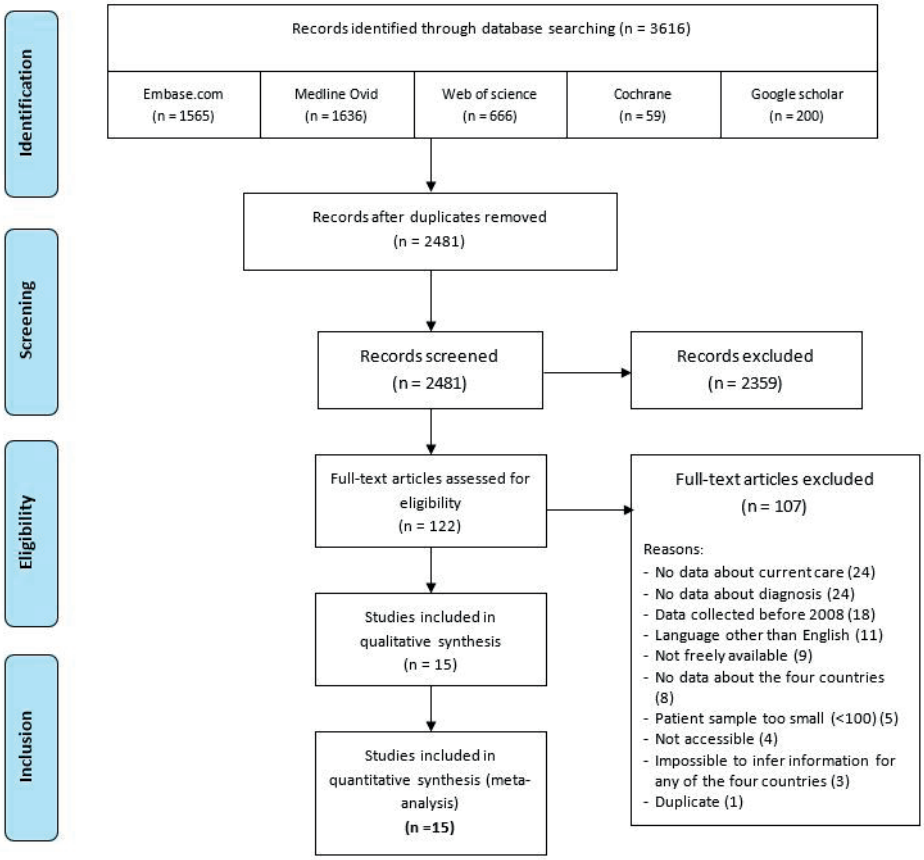
2.3.1. Search results

Figure 2.1 provides an overview of the search steps based on the Preferred Reported Items for Systematic Review and Meta-Analysis (PRISMA) guidelines [10]. The literature search using the Embase, Medline, Web of Science, the Cochrane Library and Google Scholar databases yielded 1565, 1636, 666, 59 and 200 records, respectively. After duplicates were removed, 2481 records remained for title and abstract selection, which eventually resulted in the selection of 122 records. The full-text assessment identified 15 articles that met all the inclusion criteria.

2.3.2. Study characteristics

The general characteristics of the included studies are presented in Table 2.1. Three studies were conducted in Germany [6,11,12], three in Sweden [13–15], and 10 in the UK [5,12,16–23]; no study conducted in Hungary met the inclusion criteria for the final analysis. One of the three studies conducted in Germany reported results based on a combination of German and Austrian hospitals [11]. Nevertheless, given the detailed level of information provided, the choice was made to include this study for final analysis. Another study [12] describing care in both the UK and Germany was included for analysis based on the fact that information for each country was available.

Figure 2.1 Preferred reporting items for systematic review and meta-analysis (PRISMA) flowchart.



Most selected articles were observational studies based on national registries, among which the Stroke Improvement National Audit Program (SINAP) and the Swedish stroke register that were found in 4 [17,18,20,21] and 2 studies [13,15], respectively. All the studies reported individual patient data, except the one from Jäkel et al. that was designed on data collected from telephone interviews with clinicians [12]. Since this study reported data related to TIA patients only, we decided to include it for the final quantitative synthesis. The study populations in the different publications differed slightly across studies. Most of them focused on stroke patients [5,6,13–19,21–23], two on ischemic stroke patients [11,20] and one on TIA patients [12]. Most of the studies based on a patient population database focused on adults, with the exception of one paper on children from 29 days to 15.99 years [23]. Among the adult populations studied, the mean reported ages varied slightly.

Table 2.1 Study characteristics of the selected papers

Authors	Publication year	Country of research	Health center	Number of patients	Patients' characteristics	Type of study/ study design	Origin of data	Data collection period	Study goal	Ref.
Wiedmann et al.	2014	Germany	627 hospitals	260,800	Stroke patients, Mean age: 73 Male: 50%	Analysis of collected data	Regional quality assurance projects cooperating in the framework of the German Stroke Registers Study Group	2012	To present the quality indicators for acute hospital care of stroke patients in Germany.	[6]
Singer et al.	2013	Gemany and Austria	12 stroke centers in Germany and Austria	734	Ischaemic patients undergoing EVT Median age: 70 Male: 55 % Median NIHSS at admission: 16	Observational registry study	Endostroke	January 2011 to November 2012	To focus on preprocedural imaging, patient handling and referral, as well as on different treatment modalities in mechanical recanalization.	[11]
Jäkel et al.	2012	Germany and United Kingdom	unknown	NA	Suspected TIA patients	Analysis of data collected from tele-interviews	125 interviews (number not provided for the countries of interest) of ER physicians, neurologists and geriatricians	Not reported	To gain insights into real-world global trends of the current management approaches for patients with suspected and diagnosed TIA and highlight the unmet need and areas of improvement.	[12]
Asplund et al.	2015	Sweden	all hospitals in Sweden admitting acute stroke patients (72 hospitals)	49,144	Stroke patients Mean age: 73,9 to 76,2 Male: 50,8 to 52,8% (ranges across subgroups)	Clinical data collected during hospital stay + structural data collected from a questionnaire completed by hospital staff	Riks-Stroke, the Swedish stroke register	January 2012 to December 2013	To explore to what extent differences in stroke care procedures and outcomes among university, large nonuniversity, and community hospitals exist.	[13]

Table 2.1 Study characteristics of the selected papers (*continued*)

Authors	Publication year	Country of research	Health center	Number of patients	Patients' characteristics	Type of study/ study design	Origin of data	Data collection period	Study goal	Ref.
Sundström et al.	2015	Sweden	9 emergency hospitals in Western Sweden (each with a stroke unit and the emergency medical services)	1,376	Stroke patients Mean age: 76 Male: 51%	Observational retrospective design	Data gathered from hospital and emergency medical service records, including the hospital diagnosis register	December 2010 to April 2011	To identify weak links in the early chain of care for acute stroke.	[14]
Appelros et al.	2014	Sweden	all hospitals in Sweden (80 hospitals)	320,181	Stroke patients	Observational study	Riks-Stroke, the Swedish stroke register	1995 to 2010	To describe time trends for treatment and outcome data and to discuss if changes could be attributed to quality changes in stroke care.	[15]
Bray et al.	2016	United Kingdom	199 hospitals in England and Wales	74,307	Stroke patients older than 16 Median age: 77	Nationwide, registry-based, prospective cohort study	Sentinel Stroke National Audit Programme (SSNAP)	April 2013 to March 2014	To describe the pattern and magnitude of variation in the quality of acute stroke care across the entire week.	[16]
Mallick et al.	2015	United Kingdom	all acute NHS hospitals in the South of England	139	Stroke patients, children (aged 29 days to 15.99) Group of AIS: median age 3.8, male: 51% Group of HS: median age 9, male: 62%	Prospective population-based cohort study	Case notes, electronic hospital admission databases and radiology records	July 2008 to June 2009	To assess pre-hospital and in-hospital delays to the diagnosis of AIS and HS in children in the UK and to evaluate factors influencing delays.	[23]

Table 2.1 Study characteristics of the selected papers (*continued*)

Authors	Publication year	Country of research	Health center	Number of patients	Patients' characteristics	Type of study/ study design	Origin of data	Data collection period	Study goal	Ref.
Ramsay et al.	2015	United Kingdom	51 hospitals precentralization and 44 hospitals postcentralization	38,623	Adults stroke patients Mean age: 73 Male: 49,9%	National audit	Precentralization: National Sentinel Stroke Clinical Audit Postcentralization: Stroke Improvement National Audit Program (SINAP)	Precentralization: April 2008 to April 2012 Postcentralization: April 2010 to December 2012	To explain differences in stroke mortality after centralization of care in the UK.	[17]
Campbell et al.	2014	United Kingdom	130 hospitals in England	45,726	Stroke patients Median age=77 Male: 49,1%	Prospective national clinical audit	Stroke Improvement National Audit Programme (SINAP)	April 2010 to January 2012	To identify if inequalities in the quality of care and mortality exist in contemporary stroke care in England.	[18]
Power et al.	2014	United Kingdom	24 National Health Service hospitals and 9 control hospitals in the Northwest of England	6,592	Stroke patients Male: 47,3% (control group)	Randomized trial (with one arm being current care)	Registry of discharged patients coded for stroke	July 2008 to December 2010	To determine whether hospitals participating in the QIC improved more than the control group on bundle compliance.	[19]
Bray et al.	2013	United Kingdom	106 hospitals	36,197	Ischaemic stroke adult patients Median age: 77 Male: 49%	Observational prospective cohort study	Two national clinical audits, the Stroke Improvement National Audit Programme (SINAP) and the National Sentinel Stroke Audit	April 2010 to November 2011	To estimate the relations between the organisation of stroke services, process measures of care quality, and 30 day mortality in patients admitted with acute ischaemic stroke.	[20]

Table 2.1 Study characteristics of the selected papers (*continued*)

Authors	Publication year	Country of research	Health center	Number of patients	Patients' characteristics	Type of study/ study design	Origin of data	Data collection period	Study goal	Ref.
Hunter et al.	2013	United Kingdom	after' phase: 8 HASUs in London (complemented by SUs for on-going inpatient care if necessary after 72 hours)	3,463	Stroke patients Mean age: 71,6 Male: 53% ("after" period sample)	Prospective registry (SLSR), retrospective datasets (SINAP and LMDS) and national audit (Sentinel)	South London Stroke Register (SLSR), audit from two North London hospitals, London Minimum Dataset (LMDS), Stroke Improvement National Audit Programme (SINAP), national Sentinel Stroke Audit and London Ambulance Service	Before: July 2007 to July 2008 After: July 2010 to June 2011	To investigate differences in clinical outcomes and costs between the new centralized and old models.	[21]
Palmer et al.	2012	United Kingdom	English National Health Service public hospitals	93,621	Stroke patients Mean age: 73,8 to 74,5 (weekday versus weekend) Male: 47,2 to 48,5%	Retrospective cohort study	Hospital Episode Statistics (HES)	April 2009 to March 2010	To examine the association between day of admission and measures of the quality and safety of the care received by patients with stroke.	[22]
Lazzarino et al.	2011	United Kingdom	any English public hospital	209,174	Stroke patients older than 17	Database analysis	Hospital Episode Statistics (HES)	April 2006 to March 2009	To describe the variation in use of BIS (Brain Imaging Scan (CT or MRI) among English public hospitals and identify any patient groups being excluded from appropriate care.	[5]

HASU: hyper acute stroke unit

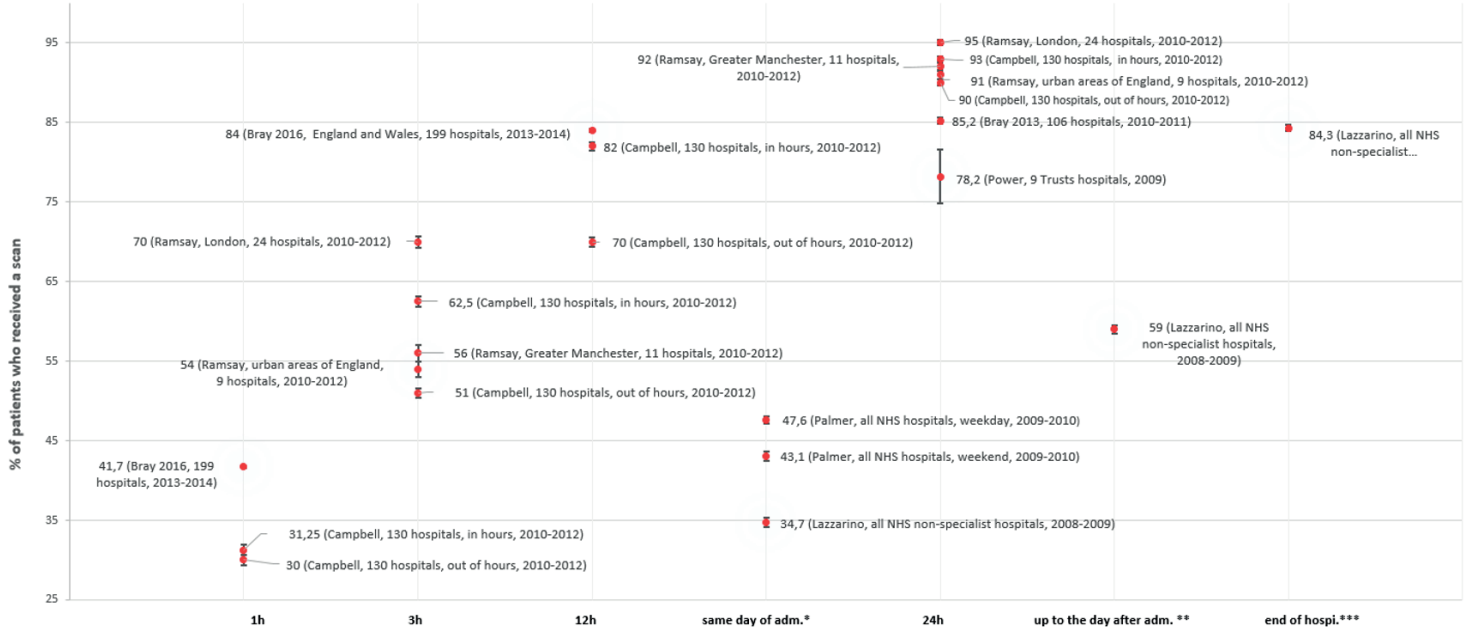
Data found in the different studies were related to a wide range of hospital groups. While two studies included all hospitals in a country [13,15], the other studies focused on a geographic or institutional subgroup of hospitals. Public hospitals were the center of investigation in two studies [5,22] while emergency hospitals were selected for analysis in one study [14]. Finally, one studies restricted the observations to stroke centers [11].

The aims widely varied across the different studies and covered a wide range of topics from a qualitative and/or quantitative perspective. The most frequent topics covered the relationship between the process of care and mortality, the pattern and magnitude of variation of care over the week, inequalities in the delivery of care and outcomes associated with a reconfiguration of care, and real-world trends in the management of acute stroke patients.

The level and amount of information regarding the type and frequency of imaging technique used are heterogeneously documented across studies. While detailed data were extracted from the studies conducted in Germany and the UK, more general information was found in the Swedish studies. Furthermore, the majority of the papers focusing on the UK reported information about the timing of the imaging workup in clinical settings. Nevertheless, after consolidation of the data originating from different authors, it was possible to present results that go beyond the findings provided by individual studies and identify patterns per country.

Studies performed in the UK often attempted to assess the quality of care by examining the use of imaging tests over time. Figure 2.2 plots the proportion of patients tested with a brain scan per time range after admission to the hospital in the UK. Data related to different investigated periods, different time categories of hospital admission (in hours or out of hours), and different geographic areas are presented and can be compared. Based on Figure 2.2, 51–70% of patients underwent a brain scan within 3 h following hospital admission and that 78–95% of the patients had undergone a brain scan within 24 h. Differences in the reported values can arise for various reasons. That is, since the results are drawn from different studies, some of the observed variations could be attributed to differences in study design, the period of investigation, geographical area, type of investigated health center and chance (due to sampling error). To minimize the effect of potential bias, focus on the results reported in a same publication might be relevant. For example, looking at the results by Ramsay, the frequency of brain scan use at 3 h varies from 56% in Greater Manchester to 70% in London which most likely reflects true differences in the way imaging is delivered to stroke patients across the UK. Ramsay also reports the frequency of brain scan use at 3 h and 24 h for two different areas. Strong variations are observed between London (70% of patients scanned at 3 h and 95% at

Figure 2.2 Proportion of stroke patients tested with a brain scan per time range over various periods and categories of settings in the UK.



The vertical bars represent the 95% confidence intervals.

*: proportion of patients tested with a brain scan during the same day of admission.

**: proportion of patients tested with a brain scan during the same day of admission or the day after.

***: end of hospitalization.

NHS: National Health Service.

Definitions applied to the time of patient admission to the hospital:

- Weekday: period from midnight on Sunday to midnight on Friday, leaving all other times defined as weekend;
- In hours: period from Monday to Friday, 8am to 6pm, leaving all other times defined as out of hours.

24 h) and urban areas of England where acute stroke services were not centralized (54% scanned at 3 h and 91% at 24 h).

Overall, both Lazzarino and Palmer reported lower proportions than the other authors, partly because they looked at the time in days after admission rather than in hours after admission. Their results are partly due to the fact that they used a timing indicator which reflects the time in days after admission rather than in hours. Thus, they reported that 35–48% of patients received a head scan during the day of admission. This low proportion might be partially influenced by the fact that some patients arriving at the hospital later in the day would receive a head scan after midnight and be registered as 'the day after' in the study. However, this consideration can probably not fully explain the low frequency that they reported. That is, by reporting 59% of patients tested during their day of admission or the day after, Lazzarino et al. present a lower frequency than Bray, Campbell, Power and Ramsay, who report 78–95% of patients scanned within 24 h. It is worth mentioning that Lazzarino's results refer to the period of 2008–2009, which might partly explain why the frequencies they report are lower than those from authors who investigated more recent periods. Furthermore, Campbell and Palmer examined the association between the time of admission during the week and the proportion of scanned patient. They report disparities between the rate of scans delivered in hours or during the weekdays compared to the rate of scans delivered out of hours or during the weekend. Their results show that patients seen out of hours or during the weekend experience longer delays to receive a scan. Finally, it is worth mentioning that no association was found between the patient populations and the reported differences in the frequency of imaging. The inclusion criteria determining the characteristics of the patients from the different studies can be found in the supplementary material 2.

Figure 2.3 provides more detailed information regarding the type of imaging technologies used in clinical practice in the UK. As such, it illustrates the frequency of usage of different modalities by subgroups of patients during different periods. CT appeared to be the most frequently used modality across the investigated periods (2008–2011), places and patient profiles. While Power reported that 78% of the stroke patients received a CT scan within 24 h of hospital admission in 2009, Hunter reported that same technology was used for 94% of the stroke patients in 2010–2011. Mallick et al. also found that CT was the most common initial imaging modality for children: in their study population, 98%of the cases of hemorrhagic stroke received a CT as first imaging workup. In contrast, MRI was the initial imaging modality for 29% of the children with ischemic stroke and only 2% of the children with hemorrhagic stroke. Another notable result presented by Hunter et al. is the relatively high proportion (68%) of stroke patients imaged with MRI in the London Hyperacute Stroke Units over 2010 and 2011. Conversely, only 2–29%

of the patients in the other subgroups were reported to be imaged with this modality. Of the stroke patients recorded in the study by Hunter et al., 63 and 49%received a CT angiography and echocardiogram, respectively.

Figure 2.3 Frequency of different imaging modalities in the UK.

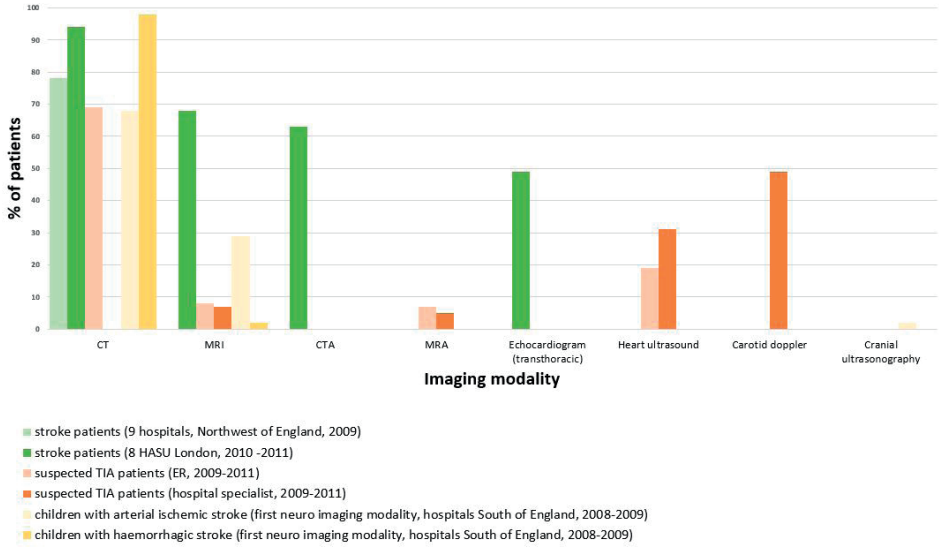
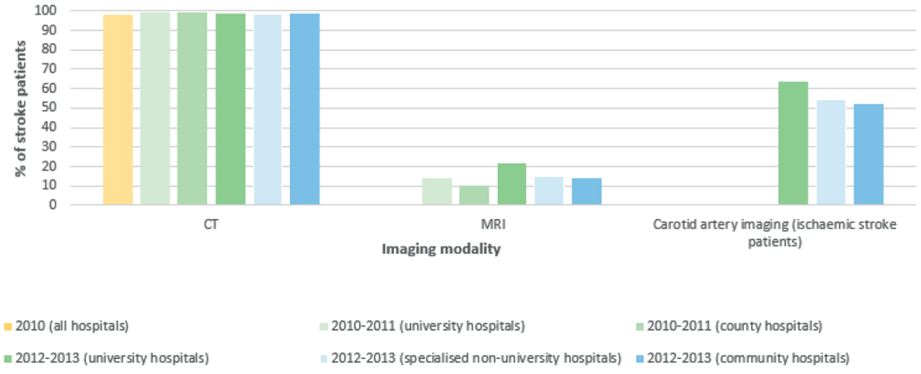


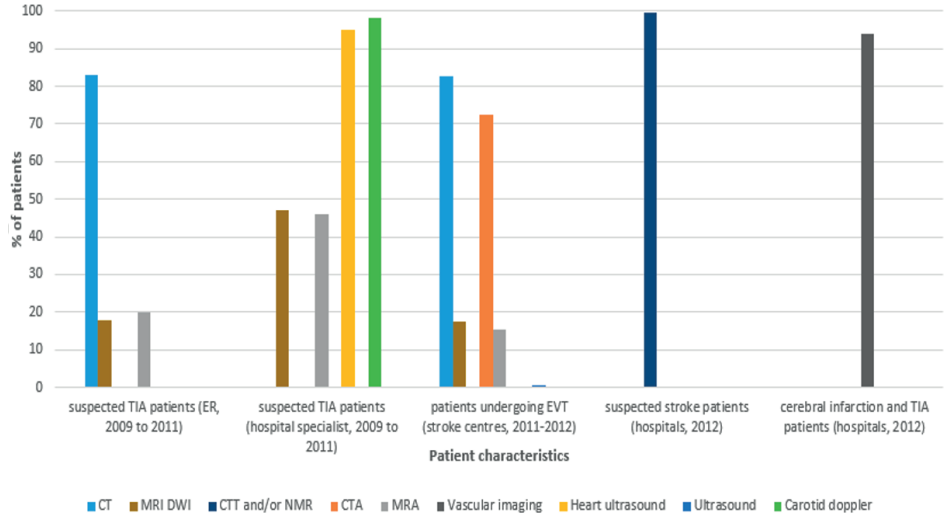
Figure 2.4 illustrates the frequency of usage of CT, MRI, and carotid artery imaging in Sweden across different settings and time periods. CT appeared to be the most reported imaging modality in Sweden from 2010 through 2013. Across the observed periods and types of hospitals, 98–99% of the patients received a CT scan. In contrast, studies reported considerably smaller proportions of patients who received an MRI in the same period. In addition, variations in the proportion of patients who received an MRI were seen, with the highest rate recorded for the years 2012–2013 and in university hospitals. Use of carotid artery imaging was characterized by intermediate frequencies of usage varying between 52 and 63% of the ischemic stroke patients over 2010 and 2011. Again, it is in university hospitals that the proportion of patients examined with carotid artery imaging was the highest. It is worthwhile to note that both Asplund and Sundström [13,14] investigated the frequencies of more than a single imaging modality. Their comparative results might be more accurate than results compared across different studies. Indeed, variations in imaging frequency could arise for various reasons such as different study populations and study methodologies. However, the individual studies investigating the frequency of CT, MRI, and carotid artery imaging found differences in the use of these imaging modalities. This observation demonstrates that the differences in frequency are caused by actual heterogeneity in clinical practice.

Figure 2.4 Proportion of stroke patients receiving different imaging modalities over various periods and categories of hospital in Sweden.



The frequency of usage of various imaging modalities per subgroup of stroke patients in Germany is depicted in Figure 2.5. Different clinical settings were covered over the years 2009–2012 in the set of selected studies. More than 99% of the suspected stroke patients were reported to have received either a CT or an MRI in 2012. The frequency of CT also appeared to exceed 80% in the groups of suspected TIA patients (emergency room setting) and endovascular stroke treatment (EVT) patients. Whereas the frequency of MRA and MRI differed substantially between the different groups of patients, the two

Figure 2.5 Proportion of subgroups of patients receiving different imaging modalities over time and categories of hospital in Germany.



MRI DWI: magnetic resonance imaging diffusion weighted imaging; CTT: cranial computed tomography; NMR: nuclear magnetic resonance.

modalities appeared to be relatively evenly used within the groups. The suspected TIA patients (hospital specialist setting) are associated with the highest MRI and MRA frequency of 47 and 46%, respectively. Within the groups of suspected TIA patients (ER and EVT patients), the rates of MRI and MRA slightly varied between 15 and 20%, similarly to the level observed in Sweden. Finally, heart ultrasound and carotid Doppler were reported for the group of TIA patients (hospital specialist) only and accounted for a rate exceeding 95%. The study by Jakel et al. shows how frequencies of imaging tests vary across clinical settings (emergency room versus hospital specialist). Their comparative results reinforce the evidence that the differences in frequency are caused by actual heterogeneity in clinical practice rather than by the differences in study characteristics.

2.4 DISCUSSION

This systematic review included published studies reporting data about the diagnosis workup of acute stroke patients in routine clinical practice in four selected European countries. Routine clinical data related to the diagnosis of stroke appeared to be unevenly reported across countries for the investigated period. The vast majority of the selected studies was conducted in the UK, while 3 papers related to the Swedish practice and 2 papers related to the German practice were identified. No study about Hungarian clinical practice was found.

The studies found in this review often reported limited or heterogeneous clinical data on the routine practice of stroke diagnosis. While most studies provided the proportion of patients receiving a brain scan across varying timeframes during the acute phase, the entire range of imaging modalities used during the diagnosis workup was reported in only one study [11]. The limitation of data found in hospital-based registries could be the reason why most studies focused on just one test [15,19]. The fact that a single head scan is the preferred strategy in some health centers where clinicians try to minimize the delay to treatment could also explain why most studies do not report data about the full range of tests. However, recent studies suggest that another approach, which consists of a more comprehensive imaging workup, is also advocated [24]. This comprehensive approach includes a combination of imaging modalities which improves patient selection for treatment. In this context, we hypothesize that the current practice is divided between the strategy of a single test and one involving a more comprehensive imaging workup. Since our analysis is constrained by the limited available data, more complete data would be needed to validate this assumption and assess the frequency at which these two approaches are used. For instance, the exhaustive list of imaging modalities routinely used for diagnosis would need to be analyzed.

Moreover, gaining insights into real-world trends of the current diagnosis approaches is hampered by the heterogeneity of the indicators used in the different studies. The imaging performance can be captured by indicators assessing the number of CT scans or MRIs. The performance is also assessed through more generic indicators tracking the number of head scans, without specifying the imaging modalities that are part of it. Likewise, time performance (the use of scans at different time points following a stroke) is assessed via a broad variety of indicators. To start with, time might be measured from symptom onset, from the patient's call for assistance or from hospital admission. Then, delays might be measured starting at any of these points in time and ending at the first head scan, the admission to the stroke unit, the first encounter with a specialist or the start of treatment. Time might be reported as a mean or median. Performance might be expressed in terms of unit of time (minutes, days, weeks) or proportion of patients tested or receiving care by a certain time threshold. This multiplicity of options found in the studies impeded a more comprehensive comparative analysis.

Furthermore, none of the included studies provided information about the time for imaging interpretation or the time between scanning and reporting. However, Mallick et al. acknowledged a study limitation in choosing the time when the diagnostic imaging is performed as an end point [23]. That is, the time of imaging differs from the time of diagnosis based on interpretation of the images and from the time of communication of the results to other clinicians. None of the 15 included studies provides the method used to report the imaging findings in clinical practice. However, the information used from an imaging test and the manner, content and level of details of imaging reports might differ across radiologists, health centers and countries. The frequency and extent to which radiologists use the reporting standards by imaging modality [25] would need to be analyzed. It might be worth investigating the frequency at which radiologists report the Alberta Stroke Program Early CT Score (ASPECTS) after performing a CT, as this indicator has proven to be useful in predicting outcomes and reperfusion [25–27].

Despite these obstacles, the strength of this review is to reveal patterns that could not be observed in individual studies. First, the consolidated results support the assumption that CT scan is the most common modality for stroke diagnosis in Germany, Sweden and the UK. Remarkably, high rates of CT scan use (from 68 to 99%) are reported across different time periods, clinical settings and patient subgroups (including children). This finding is consistent with previous studies [24] and is presumably seen because access to CT is more rapid and requires less organization, logistics and resources than access to MRI [24]. Whether the widespread use of CT is the most effective way of dealing with stroke patients is a legitimate question. Interestingly, not all patients are imaged with CT despite its wide availability. Conversely, MR imaging, despite being reported in six stud-

ies [11–14,21,23], appears to be used less frequently for the diagnosis of stroke patients in these countries.

Second, we have confronted results from different authors that reflect disparities across studies. Time, space and patient selection criteria were reported and discussed as potential reasons why these differences could arise. Given the degree of variation found in the results, it seems unlikely that changes over years alone can fully explain these differences. Besides, no association was found between the patient populations and the reported differences in the frequency of imaging. Although we cannot exclude the influence of change over years, our analysis supports the hypothesis that large variations exist in the imaging management of stroke patients across category of hospitals (university versus non-university) in Sweden, across geographical areas and across the time of day and day of week in the UK. These findings are also consistent with the conclusions from several of the individual studies and suggest that inequalities exist in the provision of stroke imaging for patients admitted out of hours, during the weekend, in non-university hospitals and in areas where acute stroke services are not centralized. According to our results, these patients are less likely to receive (timely) access to imaging.

Guidelines uniformly claim that timely brain imaging and interpretation are critical in the diagnosis and management of stroke patients. However, previous studies in the UK reported that 'more than 60% of neurosurgical centers did not have an interventional radiologist available 7 days a week… and 90% of all hospitals did not have access to computed tomography scanning 24 h per day and 7 days every week' [28]. A recent report describes the mismatch in the UK between the increase in clinical demand for CT scans (29%) and the growth in workforce (5%) from 2012 and 2015 [29]. An even more drastic gap is reported for Scotland. Overall, the UK is known to have the second lowest number of radiologists per capita across all European countries.

2.5 LIMITATIONS

Our study encountered some limitations which include the heterogeneity of studies included, the lack of data regarding the use of multiple modalities and the lack of comparative data.

For feasibility reasons, we did not include studies written in German, Swedish, and Hungarian and might have missed part of the existing literature. Besides, we did not have access to 13 studies out of 122 that were selected based on title/abstract reading. An important inherent limitation of any systematic literature review is that it only describes

what happened in the past and not what is currently taking place in clinical practice. This is worth mentioning as clinical practice in the field of stroke imaging is expected to evolve considerably fast. Whether the results we present are still relevant would need to be investigated, preferably via other complementary research methods. Finally, the proportions and frequency of imaging tests are subject to different types of bias derived from the original studies. Inconsistent coding of imaging tests within and across hospitals and data originating from both voluntary and involuntary hospital participation might affect the validity of the reported results. However, in countries where coding is being used for reimbursement purposes, it is likely that coding errors are minimal and that coding is rather consistent across hospitals. Finally, while Wiedmann reported no major differences between voluntary and non-voluntary participating hospitals [6], Asplund reported no systematic differences in data quality from the different types of hospitals [13]. Nevertheless, the value of this systematic review is that we determined what is currently known about the current imaging practices in stroke care in order to inform future modeling on the potential added value of new diagnostic modalities. Our results, by showing that access to imaging varies across settings, implies that disparities will need to be reflected in the imaging strategies included in the modeling exercises. Our results also suggest that some scanning strategies might not be relevant for a specific hospital or country.

2.6 CONCLUSION

To our knowledge, our study is the first to focus on a comparative analysis of the imaging workup used to diagnose and assess strokes across different European healthcare systems. This systematic literature review allows synthesizing the work done in the field and draws attention to the obstacles preventing a more complete analysis and synthesis. The evidence from the scientific literature is scarce and thus insufficient for an accurate between-country comparison of the imaging workup used in stroke care. Alternative research methods (i.e. survey) might be relevant to provide comprehensive data on current access to imaging for stroke patients and to inform the cost-effectiveness modeling. Further consideration should also be given to investigate the optimal imaging workup to diagnose stroke patients and select a more personalized therapy for individual patients. Given the heterogeneity of stroke care, further research is also needed to identify the causes for the variations seen in our study and to assess the quality of stroke care.

2.7 EXPERT COMMENTARY

A major weakness in clinical management lies in the slow and difficult translation and implementation of the evidence in routine clinical practice. The first proof of principle for intravenous thrombolysis arose in 1995 with the National Institute of Neurological Disorders and Stroke (NINDS) study [30]. After years of RCTs showing conflicting evidence [31] (and leaving the stroke community divided), the Cochrane review of 2014 [32] clearly demonstrated the efficacy and safety of intravenous thrombolysis. Although thrombolysis has been proven effective in acute ischemic strokes, its dissemination in routine clinical practice in various countries has been slow and limited to only a small proportion of eligible patients [33–36]. In 2014, the MR-CLEAN trial [37] provided the proof of principle for endovascular treatment and was followed by several RCTs which all confirmed the efficacy of this intervention. Evidence [38] shows that thrombectomy should be the standard of care for acute stroke caused by a large vessel occlusion and now needs to be translated in routine clinical practice across the world. While thrombolysis is relatively easy to implement, the use of thrombectomy in clinical practice faces logistical constraints that many hospitals have not overcome yet. The heterogeneity of stroke treatments delivered in clinical practice makes the need for neuroimaging different across health centers.

Furthermore, there is a lack of evidence regarding the optimal imaging approach for the diagnostic of stroke patients. Opening the artery only leads to a positive clinical outcome when viable brain tissue remains to be saved. The ideal neuroimaging method to be used to identify salvageable tissue in acute stroke patient is largely debated [39]. Although perfusion imaging is theoretically the best method to assess brain tissue viability [40], huge variations exist between commercial and academic imaging softwares. In practice, a set of clinical data (age, National Institutes of Health Stroke Scale (NIHSS), time from onset) combined to radiological data (ASPECTS, non-contrast-enhanced CT and grading of collaterals) are used by clinicians to assess tissue viability. Technology assessments of diagnostic tests for stroke are lacking [41] and would be needed to harmonize clinical practices and allow for a more systematic approach.

Further research is needed to understand the causes and drivers to heterogeneous clinical practice patterns in stroke imaging. Beyond these considerations, it would certainly be worth comparing the quality of stroke care within and between countries and to investigate to what extent the lack of harmonization creates inequalities in terms of health outcomes between patients. Since imaging tests do not directly affect long-term patient outcomes, the real impact of these tests on patients is not easily quantifiable. The benefits from imaging tests in stroke care depend not only on test performance

characteristics, but also on the prevalence of strokes and on the effectiveness of the existing treatments.

Cost-effectiveness analyses could provide a framework to compare different stroke imaging strategies through the prism of maximizing health benefit within the constraint of limited resources. There are various challenges in performing cost-effectiveness studies of stroke imaging. In stroke care, the decision-making process and resource utilization that follows imaging tests is complex and driven by many factors that can be difficult to model. Parameters (test accuracy, efficacy of treatment options, costs, health states values, etc.) are assessed based on multiple assumptions that can cause bias and inaccuracy of results. Comprehensive and complete data from large sample sizes are needed. It is not enough to capture the frequency of CT scan received by stroke patients. Studies should inform on the complete imaging workup used in stroke care and compare alternative strategies.

2.8 FIVE-YEAR VIEW

Imaging tests are valuable tools only when they influence the decision-making process and treatment choice. In current stroke care, the value of imaging is mainly found in its ability to identify and better select ischemic patients for intravenous thrombolysis or thrombectomy. The rise of these new treatment modalities has been changing the role of imaging in the stroke care pathway. Ruling out brain hemorrhage (most often by means of CT) is still needed in the first place to identify ischemic stroke patients but no longer sufficient to decide how to treat them. Information regarding the size of the occlusion should be obtained before clinicians decide to perform endovascular intervention. A CTA of the circle of Willis and ideally of the aortic arch and the neck vessels provides valuable information for treatment decision-making [42].

As mentioned above, the key challenge remains on implementing accessible and effective thrombectomy centers where both patients and relevant information must be transferred in a timely manner. This could be achieved by organizing networks of stroke care that would rely on a strong collaboration between health centers and on the definition of brain imaging standards. Thus, endovascular treatment would be performed only in high-volume centers where interventional radiologists would be available 24/24. Technical solutions already exist to allow neurologists in a given hospital to be in contact with neuroradiologists from another hospital regarding the management of an acute stroke patient [43]. Developing such collaboration would contribute to a more efficient

use of the imaging equipment and workforce and would erase part of the dramatic variations observed in stroke care.

If CT remains the mainstay of the imaging workup in stroke, it is probably because its access is fast, requires little organization, logistics, and resources. The speed of acquisition and the large volume coverage provided by modern multislice CT allow for an almost instant examination of the whole brain and for an assessment of the feeding arteries with a high spatial and temporal resolution. Some researchers have evaluated the feasibility of a 'one-stop' machine combining CT acquisition of the heart with ECG synchronization [44] and imaging of great vessels. By using this technology, they were able to inform on the origin of stroke (clot in the left atrium generating brain embolism for example) while generating a neck and brain CT image. An opportunity of development lies in hybrid systems, combining CT and angiography suite in one unique room which would minimize the time of stroke imaging work-up. Furthermore, some companies are investigating how to miniaturize CT to make it a mobile and transportable device [45]. These developments will certainly shape the future of stroke care and imply considerable changes in the logistic organization, by allowing early scan of patients from even remote places and fast transfer of data to clinicians via the Internet.

Given the shortage of radiologists, another area for development may lie in the use of artificial intelligence in stroke care. Automated techniques have already been tested for stroke diagnosis and prognosis purposes and have shown variable performances across applications [46]. Interestingly, automated diagnosis based on the assessment of the ASPECTS by means of an e-ASPECTS software has been attempted [47,48]. This software showed a non-inferior performance in comparison to conventional human assessment of the score.

Finally, photon counting is likely to be the next breakthrough in CT technology [49]. Although time-to-market is kept confidential by manufacturers, it is suggested that the technology could be commercially available within 2–4 years [49]. Assuming this timeline, early health technology assessment (HTA) [50] of SPCCT is necessary to assess its potential added-value in stroke care imaging in comparison to the currently used technologies.

Key issues

- The number and quality of studies devoted to the evaluation of the process and quality of stroke care seem to vary greatly across countries.
- Variability was found with regards to the indicators reported in the different studies. Large-scale international studies that use standardized methodological approaches are needed to assess the process of stroke care and compare it across countries.
- Ascertaining the use of imaging modalities in current stroke care requires a combination of research approaches. As such, it would be worth complementing our systematic review by an extensive and detailed international survey to clinicians in order to obtain the most recent and complete data regarding the use of imaging modalities.

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Supplemental material 1: search strategy

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Supplemental material 2: data extraction, calculation and reporting for quantitative synthesis

Presented results (proportion of patients receiving the described imaging modalities)	Authors	Reporting or calculation method	Inclusion/exclusion criteria (patient population)	Strengths and limitations regarding the accuracy of the results presented in the synthesis
Imaging in stroke patients (university, specialized nonuniversity, community hospitals) CT: 98.5%, 98.2%, 98.4% MRI: 21.3%, 14.6%, 14% Carotid artery imaging in ischemic stroke patients (university, specialized nonuniversity, community hospitals) 63.3%, 54.4%, 52.3%	Asplund et al.	As reported by the authors	Included: patients presenting with acute stroke	Strengths: data submitted to Riks-stroke were validated and no systematic differences in data quality between different types of hospitals was found.
CT in stroke patients: 98%	Appelros et al.	As reported by the authors	Included: stroke patients (the WHO definition of stroke was used)	Strengths: only cases validated by stroke physicians were included, results adjusted for a number of factors. Limitations: dropouts may create an inclusion bias.
Brain scan within 24h of admission: 85.2% [84.8 ; 85.6]	Bray et al. (2013)	Proportion reported by the authors 95% CI was calculated based on the reported mean proportion and sample size.	Included: all patients aged 18 or more years with acute ischaemic stroke Excluded: patients who are unconscious, receiving end of life care, or medically unfit (and other prespecified exclusion criteria) (excluded from denominator), patients from hospitals admitting fewer than 20 patients with acute ischaemic stroke during the covered period	Limitations: voluntary hospital participation.

Presented results (proportion of patients receiving the described imaging modalities)	Authors	Reporting or calculation method	Inclusion/exclusion criteria (patient population)	Strengths and limitations regarding the accuracy of the results presented in the synthesis
Brain scan within 1h of admission: 41.7% [41,60 ; 41,79] Brain scan within 12h of admission: 84% [83,80 ; 84,19]	Bray et al. (2016)	Proportions reported by the authors SD reported: SD: 2.8 and SD: 7.3 SE were calculated based on the SD and sample size. 95% CI were calculated based on the SE.	Included: all adult patients (aged >16 years) admitted to hospital with acute stroke (ischaemic or primary intracerebral haemorrhage)	Strengths: complete data from a national registry of clinical source (in opposition to an administrative source), validity check of the results was done to account for missing data.
(In hours, out of hours) Scan within 1h of admission: 31.25% [30.6 ; 31.9], 30% [29.4 ; 30.6] Scan within 3h of admission: 62.5% [61.9 ; 63.1], 51% [50.4 ; 51.6] Scan within 12h of admission: 82% [81.5;82.5], 70% [69.4 ; 70.6] Scan within 24h of admission: 93% [92.7 ; 93.3], 90% [89.6 ; 90.4]	Campbell et al.	Values read on the plot provided by the authors. 95% CI were calculated based on the reported mean proportions and sample sizes.	Included: stroke patients Excluded: patients with subarachnoid haemorrhage, patients who were already in hospital at time of stroke	Strengths: dataset specifically designed to capture information related to the process of acute stroke care, more accurate than administrative data. Limitations: voluntary hospital participation, differences in case ascertainment and reporting between hospitals cannot be excluded.
Head CT scan: 94% Head MRI scan: 68% CT Angiography: 63% Echocardiogram (transthoracic): 49%	Hunter et al.	As reported by the authors	Included: stroke patients Excluded: not reported	Not reported

Presented results (proportion of patients receiving the described imaging modalities)	Authors	Reporting or calculation method	Inclusion/exclusion criteria (patient population)	Strengths and limitations regarding the accuracy of the results presented in the synthesis
Imaging exams in patients with suspected TIA (Germany, UK) Reported by emergency physicians CT: 83%, 69% MRA: 20%, 7% MRI DWI: 18%, 8% Heart ultrasound: -, 19% Reported by hospital specialists CT: 83%, 69% MRA: 20%, 7% MRI DWI: 18%, 8% Heart ultrasound: 95, 31% Carotid doppler: 98%, 49%	Jäkel et al.	As reported by the authors. Data represent clinicians' perception and opinion.	Not applicable	Limitations: study designed to provide a directional indication of the current situation rather than quantitative conclusions, small sample size, subjective nature of the data, potential bias due to individual situation of the respondents.
Brain scan during the same day of admission: 34.7% [34,1;35,3] Brain scan during the same day of admission or the day after: 59% [58,5 ; 59,5] Brain scan anytime during the hospitalization: 84.3% [83,8 ; 84,7]	Lazzarino et al.	Proportions reported by the authors. 95% CI were calculated based on the reported mean proportions and calculated samples' size.	Excluded: patients who died in the same day of admission and patients younger than 17 years old.	Limitations: potential differences in quality of the administrative data across hospitals.

Presented results (proportion of patients receiving the described imaging modalities)	Authors	Reporting or calculation method	Inclusion/exclusion criteria (patient population)	Strengths and limitations regarding the accuracy of the results presented in the synthesis
First neuroimaging modality in stroke children (arterial ischaemic stroke, haemorrhagic stroke): CT: 68%, 98% MRI: 29%, 2% Cranial ultrasound: 2%, 0%	Mallick et al.	As reported by the authors	Included: children, 29 days to 15.99 years, with onset of ischemic or haemorrhagic stroke (child with acute neurological symptoms that were shown on brain imaging to be secondary to acute focal cerebral infarction or haemorrhage in a vascular distribution) Excluded: subdural or extradural haemorrhage, children with recurrent stroke	Strengths: the results presented reflect practice for half of all children in the UK.
(weekday, weekend) Brain scan during the same day of admission: 47.6% [47,2 ; 48], 43.1% [42,5 ; 43,7]	Palmer et al.	Proportions reported by the authors 95% CI were calculated based on the reported mean proportions and calculated samples' size.	Included: stroke patients	Strengths: administrative data used, which is likely to prevent bias and differences in how details from weekend and weekday are coded.
Brain scan within 24h of admission: 78.2% [74.8 ; 81.6]	Power et al.	As reported by the authors 95% CI was calculated based on the reported mean proportion and sample size.	Included: stroke patients admitted to a 'stroke unit' (minimum ten inpatient dedicated stroke beds)	Limitations: variations in data collection approaches across hospitals and variation in completeness across hospitals may create bias.

Presented results (proportion of patients receiving the described imaging modalities)	Authors	Reporting or calculation method	Inclusion/exclusion criteria (patient population)	Strengths and limitations regarding the accuracy of the results presented in the synthesis
(Comparator, Greater Manchester, London) Brain scan within 3h of admission: 54% [53 ; 55], 56% [55 ; 57], 70% [69,3 ; 70,7] Brain scan within 24h of admission: 91% [90,4 ; 91,6], 92% [91,5 ; 92,5], 95% [94,7 ; 95,3]	Ramsey et al.	Proportions reported by the authors. 95% CI were calculated based on the reported mean proportions and sample sizes.	Included: all patients diagnosed with stroke (intracerebral hemorrhage or cerebral infarction) were included, both those occurring in-hospital and outside hospital. Excluded: patients with invalid data were excluded.	Limitations: potential variations in data completeness across hospitals.
Preprocedural imaging in patients with anterior circulation ischemia or vertebrobasilar ischemia: CT: 82.5% MRI: 17,3% CTA: 72.4% MRA: 15.2% Ultrasound: 0.4%	Singer et al.	Preprocedural imaging in 489 patients with anterior circulation ischemia and 135 patients with vertebrobasilar ischemia was reported by the authors. The two samples of 489 and 135 patients were combined. The proportion of patients receiving each imaging modalities was calculated for the overall group of 624 patients.	Included: patients undergoing endovascular stroke treatment. Excluded: patients in whom vessel occlusion occurred as a complication of an angiographic procedure scheduled for other reasons (e.g., coiling of cerebral aneurysms). Patients in whom a mechanical revascularization procedure was planned but not started, i.e., due to spontaneous recanalization.	Strengths: multicentre approach.

Presented results (proportion of patients receiving the described imaging modalities)	Authors	Reporting or calculation method	Inclusion/exclusion criteria (patient population)	Strengths and limitations regarding the accuracy of the results presented in the synthesis
Imaging in patients who received a final diagnosis of stroke (university hospital, county hospitals) CT: 99%, 99% MRI: 14%, 10%	Sundström et al.	As reported by the authors	Included: intracerebral haemorrhage, unspecific brain haemorrhage, cerebral infarction and stroke not classified as infarction or haemorrhage Excluded: patients with a final diagnosis of stroke in whom symptom onset took place after admission to hospital. Patients with subarachnoid haemorrhage and extracranial haemorrhage.	Limitations: potential selection bias of observational retrospective design, data missing due to poor documentation in the emergency services and medical records.
Brain imaging (CCT and/or NMR) in patients with suspected stroke: 99.4% Vascular imaging (Doppler ultrasound and/or duplex sonography and/or digital subtraction angiography and/or magnetic resonance/ computed tomography angiography) in patients with cerebral infarction and TIA: 93.8%	Wiedmann et al.	As reported by the authors	Included: ischemic stroke, intracranial haemorrhage, subarachnoid haemorrhage, transient ischemic attack (TIA), unknown stroke type.	Strengths: no major differences observed with regard to the results between registers with mandatory participation and others registers. Limitations: possible coding errors at hospital level due to lack of consistent monitoring of the data.

3

What stroke image do we want? European survey on acute stroke imaging and revascularisation treatment

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Highlights

- CT and CTA remain the primary routine modalities of the comprehensive imaging workup in acute stroke care in Europe.
- The second line imaging test of the diagnostic workup in stroke care varies across European countries.
- Revascularisation treatments given to typical stroke patients vary considerably across European countries.
- The United Kingdom respondents reported particularly low rates of thrombectomy and high rates of intravenous thrombolysis compared to Sweden and Germany.
- A mismatch was identified between the preferred treatment and the treatment that Hungarian and UK-respondents actually administer to ischaemic stroke patients with large occlusion.

Abbreviations

ABN, Association of British Neurologists; ASPECTS, Alberta Stroke Program Early CT score; BASP, British Association of Stroke Physicians; CT, computed tomography; CTA computed tomography angiography; DWI, diffusion-weighted imaging; ESO, European Stroke Organisation; ESNR, European Society of Neuroradiology; IA, intra-arterial; IV, intravenous; IVT, intravenous thrombolysis; MR, magnetic resonance combined; MRA, magnetic resonance angiography; MRI, magnetic resonance imaging; NRSG, Neurosonology Research Group; NIHSS, National Institutes of Health Stroke Scale; SPCCT, spectral photon-counting computed tomography; TIA transient ischemic attack

Abstract

Introduction

The evolution of stroke treatment has been geared toward thrombolysis and thrombectomy, which requires quick imaging assessment. Various imaging and treatment options are available and current evidence suggests European differences in stroke care. We aimed to describe the patterns of stroke imaging and acute revascularisation therapy and examine variations across countries.

Methods

A web-based clinician survey was developed and circulated to clinicians through email distribution lists and websites of European professional societies. Statistical analyses were performed.

Results

We received responses from Sweden (21), the UK (16), Hungary (15), Germany (12) and Europe (47). Large variations are observed in revascularisation treatment: German respondents report that 81% of their ischaemic stroke patients diagnosed with a large vessel occlusion within 4.5 h receive intravenous thrombolysis and thrombectomy, compared to 12% reported by the UK-respondents. For patients diagnosed with an extensive ischaemic stroke within 2 h from onset, 75% of UK-respondents state thrombectomy as their preferred revascularisation treatment, but only 13% report to use it. Computed Tomography (CT) is reported as the most widely used first imaging test (for 81% to 93% of patients across geographic areas), while Magnetic Resonance Imaging (MRI) is a distant second.

Conclusion

The diagnostic workup and, to a greater extent, the revascularisation treatments of typical stroke patients vary considerably across European countries. This study reinforces the need to compare the quality of stroke care in terms of process and outcomes between countries. Research is also needed to investigate the cost-effectiveness of second-line imaging strategies in acute stroke care.

3.1 INTRODUCTION

The rapid evolution of stroke treatment over the past years has been geared toward thrombolysis and more recently thrombectomy, both of which have been proven highly effective [1]. These treatments require a quick differentiation between ischaemic and haemorrhagic brain damage, as well as perfusion impairment. This makes neuroimaging essential in the acute phase. Computed Tomography (CT) combined with CT Angiography (CTA) or Magnetic Resonance (MR) combined with Magnetic Resonance Angiography (MRA) form the imaging standard of diagnostic workup. However, other imaging technologies exist and new technologies emerge: dual energy CT and, more recently, spectral photon-counting CT (SPCCT) are innovative imaging tools expected to improve treatment decision-making in stroke in emergency settings by better quantifying brain perfusion impairment [2]. To assess the relative value of innovation, current clinical practices need to be assessed. Much of what is known about clinical practice regarding stroke care is based upon registry data (for instance Riksstroke in Sweden [3] and SSNAP in the UK [4]). As far as imaging is concerned, the SSNAP registry reports the number of patients scanned within certain time windows without describing the sequence of diagnostic modalities. Furthermore, these registries concern heterogeneous group of (ischaemic) stroke patients and are limited to specific countries. Evidence suggests differences in stroke care and outcomes within European countries [5]. The scarcity of and the need for international comparisons and databases have been pointed out by different authors, suggesting that variations in care need to be understood better.
In this context, we developed and used an online survey aiming to describe current clinical practice in acute stroke care in Europe and to examine variations between countries. The focus was made on diagnostic imaging technologies and the use of revascularisation treatment.

3.2 METHOD

Design

In order to assess clinical practice in Europe regarding acute stroke care, an online clinician survey was developed, pilot-tested and distributed. The survey questions were formulated based on expert opinion and feedback collected from a European expert panel, which included five neurologists, two radiologists and one neuro-radiologist. A pilot phase was conducted before the survey was launched in October 2016. The survey was conducted using the online software "Google form" and was made available online. The target population included neurologists, stroke physicians, neurointerventionalists,

neuroradiologists, neurosurgeons and emergency physicians (including those completing their specialisation). Because we were interested in examining a range of healthcare systems, Germany, Hungary, Sweden and the United Kingdom were chosen as main target countries. Whereas Sweden is known for its early adoption of medical technologies, Hungary tends to be a late adopter. Besides, the UK is of major interest for its publicly funded system while Germany is characterised by its decentralised healthcare organisation in which private practitioners play a relatively important role. No financial incentive was offered to participants and survey completion was voluntary.

Structure

A closed and structured format in English was chosen to enable clinicians to select their responses among multiple predefined choices. An introduction provided the framework of the study and was followed by general questions regarding the respondents' work setting. Subsequently, respondents were asked about the routine imaging workup and treatment used in their centre and the proportion of stroke patients receiving each of these modalities. Section three contained questions about the imaging modalities used to diagnose stroke and make therapy decisions. In sections four and five, respondents were asked about the treatment modalities used in acute stroke care in their centre. In section six, respondents were asked about the typical follow-up imaging strategy used after reperfusion therapy. We investigated the clinicians' opinion towards progress in section seven and requested them to report the guidelines they use in section eight. The questions focused on different patient profiles that are summarised in Table 3.1. The survey questions can be found in supplement.

Table 3.1 Patient profiles as defined in the survey

Case	Patient profile	Procedure	Maximum time from symptom onset to procedure (hours)
A	Suspected of acute stroke	Initial imaging for differential diagnosis	-*
B	With moderate or severe ischaemic stroke	Second imaging test (after differential diagnosis imaging)	4
C	With minor ischaemic stroke or TIA		-*
D	With haemorrhagic stroke		
E	With ischaemic stroke and large vessel occlusion	Choice of revascularisation treatment	4.5
F	Male aged 65, admitted with complete aphasia, NIHSS score of 14. CTA at admission showed an occlusion of the first segment of the left middle cerebral artery (M1). ASPECTS score was 5. No contraindication for thrombolysis or thrombectomy		2
G	Who received reperfusion therapy	Follow-up imaging after reperfusion	48

ASPECTS: Alberta Stroke Program Early CT score.
NIHSS: National Institutes of Health Stroke Scale.
TIA: transient ischemic attack.
* : timing not specified in the survey.

Dissemination

The online survey link was circulated through email distribution lists and websites of national and European professional societies. Given our interest in the four different health care systems, the British Association of Stroke Physicians (BASP), the Hungarian Stroke Society and the Swedish Acute Neurology Society invited their members to participate in the survey through personal emails. The European Society of Neuroradiology (ESNR) and the Association of British Neurologists (ABN) advertised the survey to their members via their November newsletter. The Neurosonology Research Group (NSRG) and the Hungarian Stroke Society encouraged their members to participate by circulating the survey through their website.

To boost participation, we adopted a complementary strategy and sent emails to the department leads of 39 Hungarian and 80 German stroke centres with the request to invite their personnel to participate in the survey. In addition, we sent an email containing the survey link to 20 English and 37 Swedish clinicians whose contact information was found on the internet. Up to three reminder emails were sent to potential respondents.

Statistical analysis

Reported percentages of patients receiving imaging or treatment modalities and percentages of clinicians reporting to use different treatments were extracted from the clinicians' responses. Mean percentages were calculated for five geographic areas: the four countries and the whole group of European countries (including the four countries). The 95% confidence intervals surrounding the mean estimates were computed using the percentile of the bootstrap distributions [6]. This involved randomly resampling the original samples with replacement 500 times, which corresponded to the number of replications needed to ensure stability and accuracy. Each bootstrapped sample yielded a bootstrap statistic (e.g. mean frequency). The bootstrap distribution was computed from the 500 bootstrap statistics, per geographic area. Frequencies of CT versus MRI usage were compared using T-tests and between- country comparisons of imaging and treatments were derived using one-way anova tests in SPSS (version 23).

3.3 RESULTS

We received responses from 172 clinicians. Of those respondents, 55 dropped out of the survey before completing 70% of the questions (up to question 14c), corresponding to a drop rate of 32%. Data from these 55 respondents as well as data from 6 non-European clinicians were taken out of the analysis. Among the 111 remaining respondents, 21 were from Sweden, 16 from the UK, 15 from Hungary, 12 from Germany and 47 from

19 other European countries. Details about the respondents' characteristics and work environment can be found in Table 3.2.

Table 3.2 Respondent characteristics

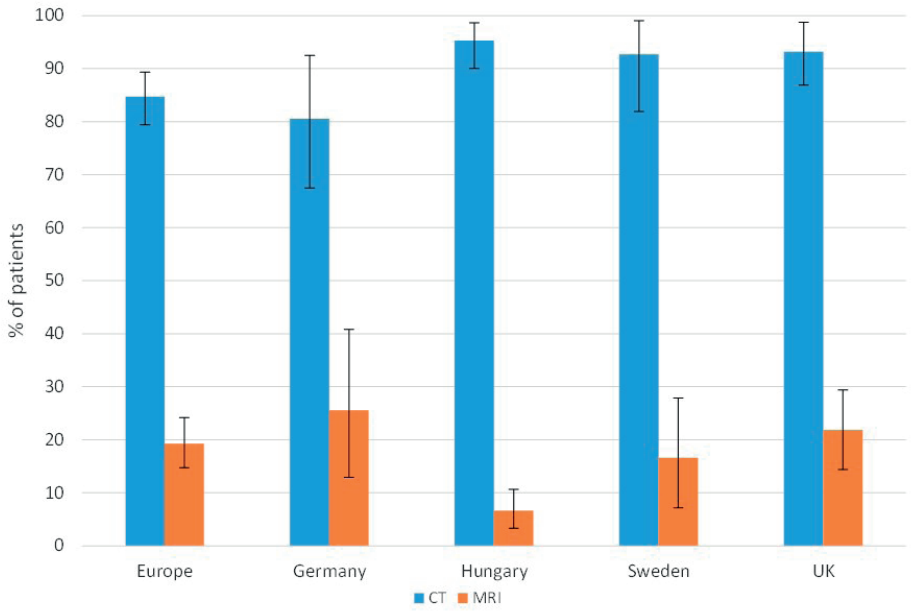
	Number	%
Respondents' characteristics	111	100
Country		
Sweden	21	19
UK	16	14
Hungary	15	14
Germany	12	11
Other countries	47	42
Specialty		
Neuroradiologist	30	27
Neurologist	24	22
Stroke physician	17	15
Neurologist and stroke physician	16	14
Neurointerventionalist and neuroradiologist	8	7
Neurointerventionalist	7	6
Completing specialty in neurology	5	5
Department chairman, radiologist, rehabilitation specialist	4	4
Year of completion of main specialty		
1976-1985	5	4
1986-1995	23	21
1996-2005	18	16
2006-2015	53	48
2016-2020	12	11
Funding system		
Public	104	94
Private	7	6
Teaching category		
Academic hospital	76	68
Non-academic hospital	35	32
Stroke unit	102	92

Diagnosis

First line imaging test for differential diagnosis

Non-contrast-enhanced brain CT is reported as the primary routine modality used to diagnose suspected stroke patients (profile A) and differentiate ischaemic from haemorrhagic strokes (Figure 3.1). On the basis of the responses, it is obtained for more than 80% of the patients in each of the four different countries and Europe as a whole and used significantly more than MRI ($p < 0.001$). Hungary shows the most extreme differences between the frequency of CT usage versus MRI usage ($p < 0.001$).

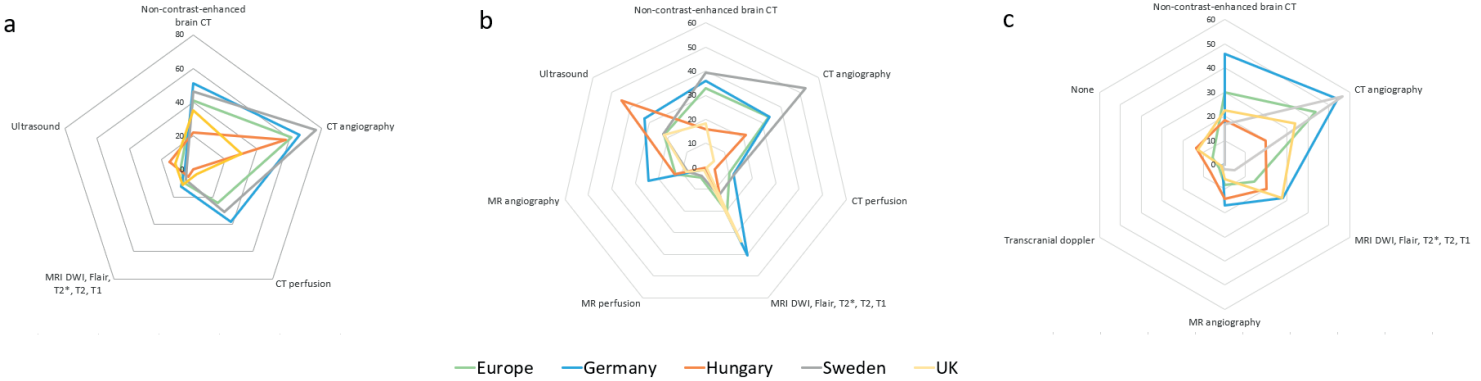
Figure 3.1 Differential diagnosis of stroke type (haemorrhagic or ischaemic): CT versus MRI usage with 95% confidence intervals



Second line imaging tests for prognosis and treatment choice

Following the diagnosis of moderate to severe ischaemic stroke within 4 h of onset (profile B), vascular imaging is reported to be routinely obtained as a second-line modality to evaluate the prognosis and determine the treatment choice (Figure 3.2a). According to the clinicians' responses, CTA is performed in 62% of the patients in Europe, 30% of the patients in the UK, 58% of the patients in Hungary, 66% of the patients in Germany and 79% of the patients in Sweden. Moreover, non-contrast-enhanced CT and CT perfusion play a relatively important role in this phase while MRI (DWI, Flair, T2*, T2, T1) and ultrasound appear to be less frequently used. Finally, MR perfusion and MRA are used for an average of 4% and 9% of patients across Europe, respectively (results not shown). Figure 3.2b reports the frequencies of different imaging modalities for patients diagnosed with a TIA or minor stroke (profile C). It illustrates the degree of between-country heterogeneity and the large combinability of imaging tests used in second line. The results show that CTA is obtained for 53% of Swedish patients but for only 4% of English patients. While ultrasound is obtained for 44% of the patients in Hungary, it is used for an average of 22% of the patients in Europe.

Figure 3.2 Proportion of patients receiving a second-line imaging test



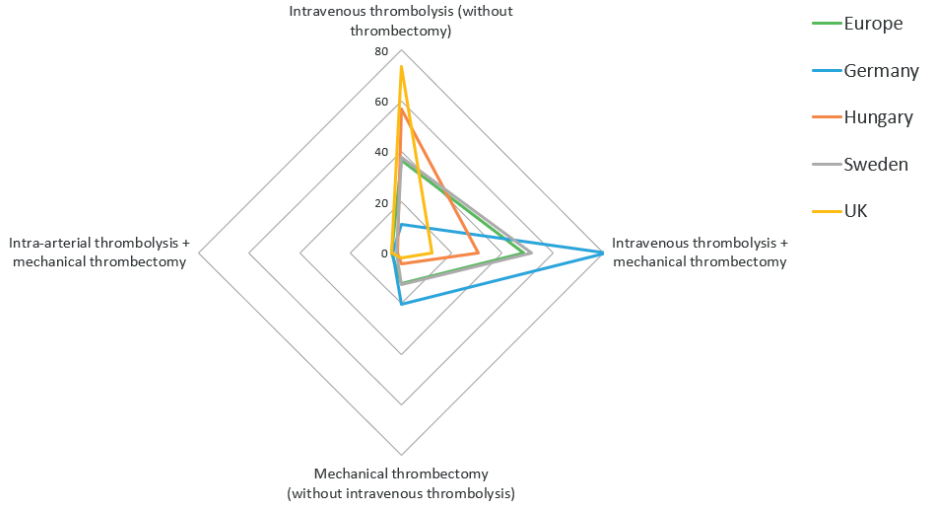
3.2a: moderate to severe ischaemic stroke (within 4 h of onset) 3.2b: TIA or minor stroke 3.2c: haemorrhagic stroke.

Similarly, CTA is routinely performed as the second imaging test, after the diagnosis of a haemorrhagic stroke (profile D) (Figure 3.2c). Substantial proportions of the European patients also receive a brain CT (30%) or an MRI (14%). Remarkably, the German respondents report to perform 48% more imaging tests than their European peers (1.52 versus 1.03) following the initial diagnosis of a haemorrhagic stroke.

Treatment

Figure 3.3 shows the frequencies of revascularisation treatments given to ischaemic patients diagnosed with a large occlusion and within 4.5 h of symptom onset (profile E). For these typical patients, German respondents reported to use mechanical thrombectomy significantly more often than the UK-respondents ($p = 0.017$) and Hungarian respondents ($p = 0.044$). Interestingly, the UK shows the lowest rate of thrombectomy (19% of the patients), in favour of the highest rate of thrombolysis (80% of the patients) amongst the investigated geographic areas. With 73% of English patients from profile E receiving it, intravenous thrombolysis (IVT) is significantly more used in the UK than in Europe ($p < 0.001$), Sweden ($p < 0.001$) and Germany ($p < 0.001$).

Figure 3.3 Proportion of patients (profile E) receiving revascularisation treatment

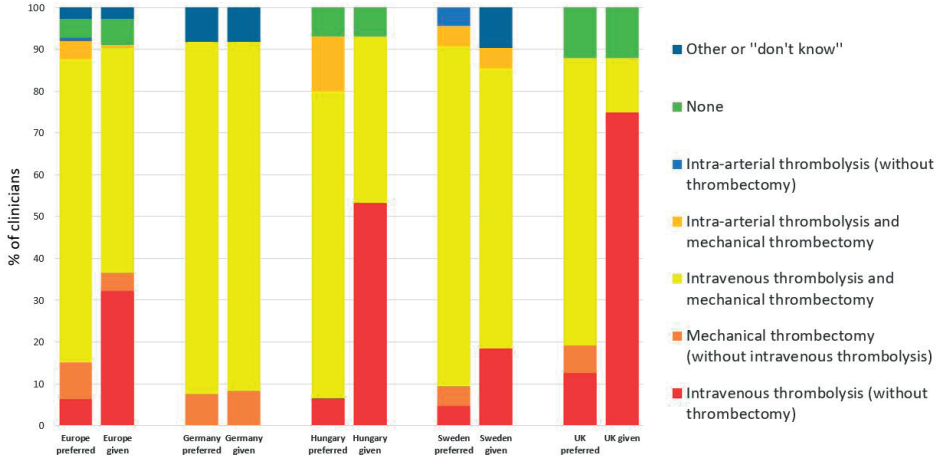


The time window of revascularisation treatments varies substantially between and within countries. In Germany, while 33% of the respondents report to use mechanical thrombectomy up to a maximum of 6 h after symptom onset, 50% perform this treatment up to 7–10 h. A similar variation can be observed in Sweden. In addition, 10% of the clinicians in Europe do not use thrombectomy at all and this proportion increases to 20% and 24% in Hungary and in the UK, respectively.

Detailed clinical case

During the survey, the respondents were asked to indicate their choice of revascularisation treatment for a typical patient belonging to profile F (see Table 3.1). The respondents had to indicate both their preferred treatment and the actual treatment they would provide in their health centre. Most respondents in Europe overall (73%) stated that IVT combined with mechanical thrombectomy was the preferred treatment option; this was also true in each of the four countries (Figure 3.4). While the German and Swedish practice tended to be aligned on this preference, wide variations were observed between the preferred and current options in the UK (56 percentage points), in Hungary (33 percentage points) and, to a lesser extent, in Europe (19 percentage points). In these three areas, mechanical thrombectomy was less frequently used than IVT.

Figure 3.4 Clinical case - preferred treatment versus given treatment



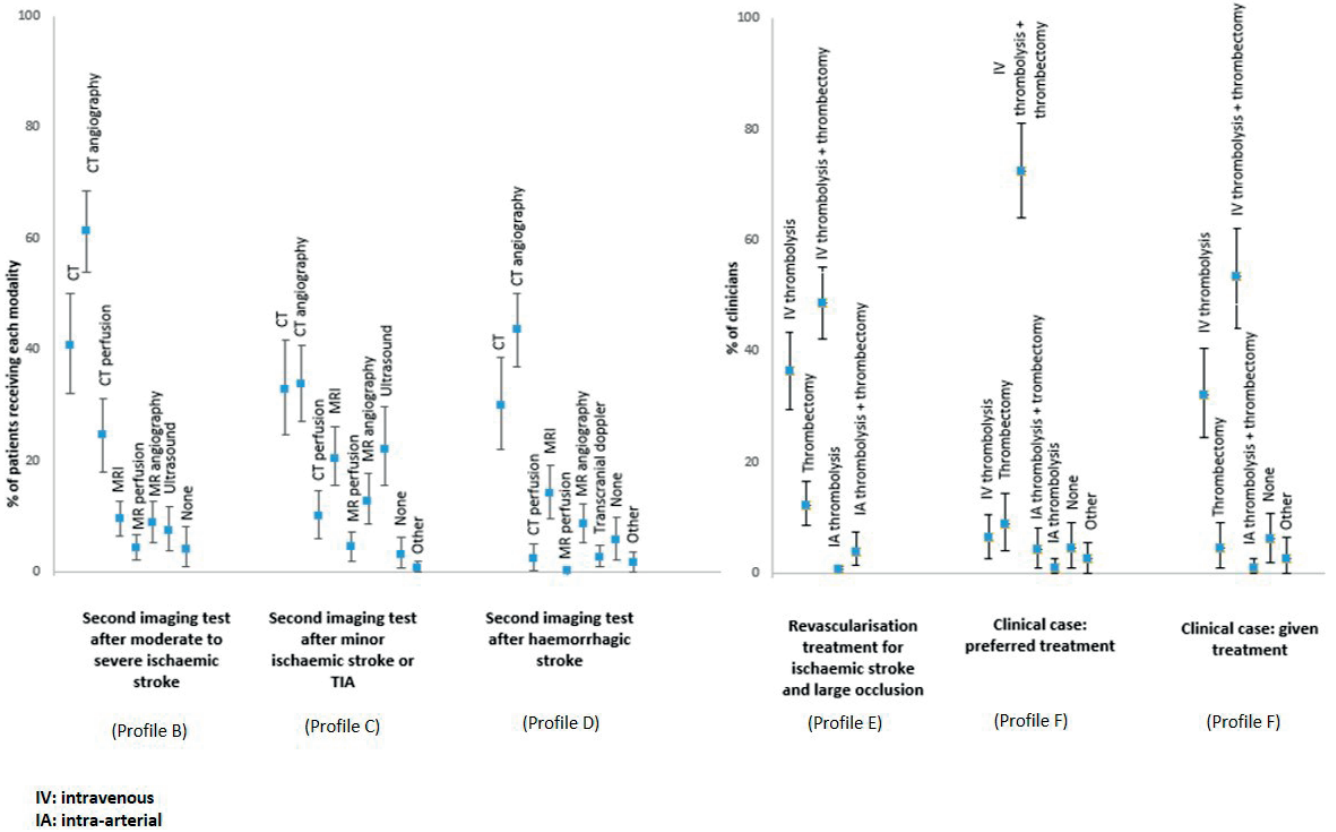
Follow-up imaging

The vast majority of the European clinicians (93%) responded that follow-up imaging was performed for all patients from profile G. After reperfusion therapy, 82% of the European patients receive a follow-up CT. While MRI also plays a relatively important role in this clinical phase (27% of the European patients receiving it), CTA, MRA and transcranial doppler are less frequently used (for 9%, 19% and 11% of the patients respectively).

Confidence analysis

We calculated the uncertainty around the means presented in Figure 3.2 , 3.3 and 3.4 (Figure 3.5). Even when we consider this uncertainty, differences shown in the previous figures appear to be statistically significant except regarding the instances for which confidence intervals overlap.

Figure 3.5 Estimated relative frequency of use of imaging modalities and treatment in acute stroke care in Europe with 95% confidence intervals by patient profile



IV: intravenous
IA: intra-arterial

Summarizing the above, on the basis of the responses received, non-contrast-enhanced brain CT is the first-line routine imaging modality to differentiate ischaemic from haemorrhagic patients. Once a moderate or severe ischaemic stroke is diagnosed, vascular imaging (CTA) is predominantly used for acute therapeutic decisions across the investigated areas. Once a TIA or minor stroke is diagnosed, a CTA and ultrasound are almost equally likely to be obtained as second-line test. Haemorrhagic stroke patients are likely to receive either a CT (brain CT or CTA) or MR (MRI or MRA) scan. The imaging workup for minor stroke/TIA and haemorrhagic stroke patients tends to be less harmonised than for severe strokes across the areas. A substantial proportion of patients receives a comprehensive imaging work-up which includes a combination of imaging tests. Finally, non-contrast-enhanced brain CT remains the routine follow-up modality after revascularisation treatment of ischaemic stroke.

3.4 DISCUSSION

To the best of our knowledge, this study presents the first online survey aiming to describe current clinical practice in acute stroke care in Europe and to examine potential variations between countries.

Main findings

This survey revealed that variation in acute stroke care is limited regarding the first line imaging test (differential diagnosis) but increases at later stages of the imaging workup and in the choice of treatment. CT is the mainstay of the stroke imaging workup in the initial phase and this observation holds in later phases of acute care. This finding is presumably seen because access to CT is more rapid and requires less organisation, logistics and resources than access to MRI and is consistent with previous studies [7]. Whether the widespread use of CT is the most effective way of dealing with stroke patients is a legitimate question. Interestingly, clinicians reported that not all their patients are imaged with CT despite its wide availability.

Besides, our study shows that a comprehensive imaging workup is used in stroke care which includes a combination of vascular (CTA and MRA), core (brain CT and MRI) and penumbra imaging (CT and MR perfusion). However, our results suggest that stroke imaging is less frequently used in Hungary and the UK compared to Germany, Sweden and the rest of Europe. German clinicians appear to image their patients substantially more often than their European peers do, both during the second-line imaging phase and during the follow-up imaging phase. Ideally, the diagnostic accuracy or prognostic value of an imaging modality should determine its use in clinical practice. However, recent

evidence suggests that within 6 h from symptom onset, perfusion imaging does not help in identifying patients who will not benefit from endovascular treatment [8]. This suggests that the imaging workup used by many clinicians in stroke care is not optimal for treatment decisions.

In addition to finding variations in the imaging workup between countries, we also found variations in the choice of revascularisation treatment for ischaemic patients. The main factor of between-country practice variation is related to thrombectomy among the severe stroke patients receiving treatment within 4.5 h of symptom onset: the lowest rates are reported in the UK and the highest in Germany. This observation shows that European stroke guidelines are unequally implemented across countries. Indeed, the European Stroke Organisation (ESO) and three other European associations have recommended mechanical thrombectomy, in addition to IVT, to treat stroke patients with large artery occlusions in the anterior circulation, up to 6 hours after symptom onset [9]. Furthermore, they have recommended mechanical thrombectomy as first-line treatment in large vessel occlusions when IVT is contraindicated. Interestingly, the results of the SSNAP national stroke audit performed in the UK were released in December 2016 [4]. According to these results, only 18% of the patients have access to mechanical thrombectomy on-site, 50% of them can access the treatment by referral to another site and 32% do not have access to it at all. Our survey results are consistent with these findings. Their audit reports that only 83 consultants perform thrombectomies and mentions that the service is only available during the week (not in the weekend). Logistical and workforce issues are pointed out as causes for the limited availability of this procedure [10]. Further research would be needed to identify barriers to thrombectomy.

The mismatch we identified between the clinicians' preferred treatment and the treatment they actually administer might be explained by the fact that thrombectomy is not sufficiently available, especially in the UK and Hungary. Furthermore, the maximum time window applied to perform revascularisation treatment is not harmonised among clinicians. Although treatment has been proven beneficial within a certain amount of time from the onset (for instance within 4.5 h for IVT [11]), large practice variations are seen, both within and between countries.

This paper adds to the existing literature in two ways. First, it informs about the diagnostic and treatment workup for specific groups of stroke patients and, as such, provides a different level of information compared to registries that focus on the whole group of (ischaemic) stroke patients. Second, it provides insight into the diagnostic and treatment pathway for stroke care in Germany and Hungary. In these two countries, no (or only very limited) information related to stroke care is publicly available.

3.5 LIMITATIONS

As a limitation to our study, we acknowledge that a limited number of responses was received. Our survey faced the inherent disadvantage of any survey, which is the challenge to reach respondents. Since most of the professional associations advertised the survey on their website or via their newsletter, we assume that only a few clinicians actually found the survey link and were given the opportunity to fill in the web-based questionnaire. Generalizability might be limited by survey-typical selection bias and further research is needed to confirm and generalise our findings. Yet, our results appeared to be statistically significant and consistent with previous findings and the survey method allowed to explore current stroke imaging practices in details. To the best of our knowledge, this is the first study to provide that level of insight in European stroke imaging practices and thus makes an important contribution to the literature.

3.6 CONCLUSION

The diagnostic workup and, to an even greater extent, the revascularisation treatments of typical stroke patients vary considerably across European countries. However, CT and CTA remain the primary routine modalities of the comprehensive imaging workup. Further research is needed to identify the causes for the variations seen in our study, the barriers to treatment and to compare the quality of stroke care between and within countries in terms of both process and outcomes. Further consideration should also be given to investigate the most cost-effective second-line imaging workup to diagnose stroke patients. This knowledge may be used as input in evaluations comparing the potential added value of new imaging modalities with the ones currently used in clinical practice.

Ethical approval

No financial incentive was offered to participants and survey completion was voluntary. Completion of the survey by participants was established as a means of consent to participate. We received an approval by the board of the Medical Ethics Committee from the Erasmus Medical Center of Rotterdam, The Netherlands (Medisch Ethische Toetsings Commissie) to conduct this study, under reference MEC-2017–537.

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SUPPLEMENTAL MATERIAL

The survey is still available at the following URL: https://docs.google.com/forms/d/e/1FAIpQLSfDPYnvFIA29Uydyhhwaqz7Xu5chpLoFAcK9Zr12H-X0BxRtg/viewform?fbzx=7466614251363575000

SURVEY QUESTIONS

GENERAL QUESTIONS

Q1a: In what COUNTRY is your health centre located?

Q2: In what CITY is your health centre located?

Q3: What is your exact function?

Q4: When did you or will you complete your main specialty?

Q5: What is the teaching category of your health centre?

Q6: Is your health centre publicly or privately funded?

Q7a: How many ISCHEMIC DIAGNOSED STROKE PATIENTS does your health centre receive annually?

Q7b: How many HEMORRHAGIC DIAGNOSED STROKE PATIENTS does your health centre receive annually?

Q8: Is there a stroke unit in your health centre?

Q9a: WHAT IMAGING TECHNIQUES are available for use in the emergency department of your main health centre for all acute cares and WHEN are they available?

Q9b: If you marked "other imaging test(s)" in the previous question, please describe the modality used.

IMAGING MODALITIES

Q10a: Among all suspected stroke patients in your health centre, what is the imaging modality used to establish the DIFFERENTIAL DIAGNOSIS of ischemic versus hemorrhagic stroke? For each imaging modality used, please indicate the proportion of the patients that undergo that modality.

Q10b: If you marked "other imaging test(s)" in the previous question, please describe the modalities used.

Q11a: In your health center, when a patient is diagnosed with a MODERATE TO SEVERE ISCHEMIC STROKE based on the first imaging test and within 4 hours of onset, for what proportion of patients do you use the following second imaging test(s) for the ACUTE THERAPEUTIC DECISION MAKING? (more than 1 answer is possible).

Q11b: If you marked "other imaging test" in the previous question, please describe the modality used.

Q12a: In your health center, when a patient is diagnosed with a MINOR ISCHEMIC STROKE OR TIA based on the first imaging test, for what proportion of patients do you use the following second imaging test(s) for the ACUTE THERAPEUTIC DECISION MAKING? (more than 1 answer is possible).

Q12b: If you marked "other imaging test" in the previous question, please describe the modality used.

Q13a: In your health center, when a patient is diagnosed with a HEMORRHAGIC STROKE based on the first imaging test, for what proportion of patients do you use the following second imaging test(s) for the ACUTE THERAPEUTIC DECISION MAKING? (more than 1 answer is possible).

Q13b: If you marked "other imaging test" in the previous question, please describe the modality used.

TREATMENT

Q14a: For patients diagnosed with an ISCHEMIC STROKE AND A LARGE OCCLUSION, within 4.5 hours from symptom onset, what revascularization treatment method(s) do you choose and for what proportion of patients? (more than 1 answer is possible).

Q14b: What is your maximum time window of revascularization treatment for the following options? (Please fill in at least the 5 first rows)

Q14c: If you marked ''other treatment(s)'' in one of the 2 previous questions, please describe the modality used.

TREATMENT - CLINICAL CASE

A 65-year-old male patient presenting with a suspected stroke was admitted with COMPLETE APHASIA and with a NIHSS* score at 14.

A computed tomography (CT) angiogram scan performed at admission showed that a M1 segment of the left middle cerebral artery was occluded and the patient's ASPECTS** score was 5.

There was no contraindication of thrombolysis or thrombectomy.

*National Institutes of Health Stroke Scale ''NIHSS'' is a 15-item neurologic examination stroke scale used to evaluate the effect of acute cerebral infarction on the levels of consciousness, language, neglect, visual-field loss, extraocular movement, motor strength, ataxia, dysarthria, and sensory loss. An observer rates the patent's ability to answer questions and perform activities. Ratings for each item are scored with 3 to 5 grades with 0 as normal while a higher score is indicative of some level of impairment. The maximum recordable NIHSS score is 42. NIH Stroke scores > 22 are considered very significant and may predict increased complication risk.

**Alberta Stroke Program Early CT Score ''ASPECTS'' is a 10-point quantitative topographic CT scan score. A normal CT scan receives ASPECTS of 10 points. A score of 0 indicates diffuse involvement throughout the middle cerebral artery territory. 1 point is deducted from the initial score of 10 for every region involved. A sharp increase in dependence and death occurs with a score of 7 or less.

Q15a: For this specific case, what would be your PREFERRED treatment at 2 hours from symptom onset? (Please note, thrombectomy may remain your preferred treatment option even if no neurosurgeon is available in your health centre)

Q15b: For this specific case, what would be the treatment GIVEN in your health centre at 2 hours from symptom onset?

FOLLOW-UP IMAGING

Q16: Do you routinely perform follow-up imaging after reperfusion therapy and within the 48 hour window after symptom onset?

Q17: For what proportion of patients do you undertake follow-up imaging with the proposed modalities below?

YOUR OPINION ON PROGRESS

Q18a: In your opinion, which are the main clinical stages where progress in imaging capabilities could improve the clinical practice, improve patient outcomes or decrease healthcare costs? Please prioritize (1: most important stage, 3: least important phase)

Q18b: If you wish, please clarify your answer here.

GUIDELINES

Q19: What guidelines do you use as a reference? (more than one answer is possible)

Interested in the SPCCT research project?

Q20: Are you interested in receiving the results of the survey and/or participating in a subsequent phase of the SPCCT research project?

4

Exploring the cost-effectiveness of mechanical thrombectomy beyond six hours following advanced imaging in the UK

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Abstract

Background and Purpose

In the United Kingdom, mechanical thrombectomy (MT) for acute ischemic stroke patients assessed beyond 6 hours from symptom onset will be commissioned up to 12 hours provided that advanced imaging (AdvImg) demonstrates salvageable brain tissue. While the accuracy of AdvImg differs across technologies, evidence is limited regarding the proportion of patients who would benefit from late MT. We compared the cost-effectiveness of 2 care pathways: (1) MT within and beyond 6 hours based on AdvImg selection versus (2) MT only within 6 hours based on conventional imaging selection. The impact of varying AdvImg accuracy and prior probability for acute ischemic stroke patients to benefit from late MT was assessed.

Methods

A decision tree and a Markov trace were developed. A hypothetical United Kingdom cohort of suspected stroke patients aged 71 years with first event was modeled. Costs, health outcomes, and probabilities were obtained from the literature. Outcomes included costs, life years (LYs), quality-adjusted life years (QALYs), and incremental cost-effectiveness ratios. Probabilistic sensitivity analyses were performed. Various scenarios with prior probabilities of 10%, 20%, and 30%, respectively, for acute ischemic stroke patients to benefit from late MT, and with perfect accuracy, 80% sensitivity, and 70% specificity of AdvImg were studied.

Results

Incremental cost-effectiveness ratios resulting from our deterministic analyses varied from $8199 (£6164) to $49 515 (£37 229) per QALY gained. AdvImg accuracy impacted the incremental cost-effectiveness ratio only when its specificity decreased. Over lifetime horizons, all scenarios including late MT improved QALYs and LYs. Depending on the scenario, the probabilistic sensitivity analyses showed probabilities varying between 46% and 93% for the late MT pathway to be cost-effective at a willingness to pay threshold of $39 900 (£30 000) per QALY.

Conclusions

Late MT based on AdvImg selection may be good value for money. However, additional data regarding the implementation of AdvImg and prior probability to benefit from late MT are needed before its cost-effectiveness can be fully assessed.

4.1 INTRODUCTION

Recently, 2 prospective randomized control trials demonstrated superior health benefits of mechanical thrombectomy (MT) beyond 6 hours from symptom onset (late MT) plus standard medical care versus standard medical care alone in acute ischemic stroke (AIS) patients. Patient selection was based on advanced imaging (AdvImg), namely perfusion imaging with computed tomography (CT) or magnetic resonance [1,2]. As new evidence emerged, policymakers updated their recommendations and the National Health Service (NHS) England issued a document in March 2018 announcing that MT would be routinely commissioned provided it can be achieved within 6 hours of the onset of stroke [3]. Furthermore, NHS England will commission MT until 12 hours where AdvImg indicates substantial salvageable brain tissue [3].

In the vast majority of the randomized clinical trials establishing the benefit of MT in AIS patients, CT followed by CT angiography (CTA) were the imaging modalities used to assess the brain tissue and intracranial vessels [4]. In the United Kingdom (UK), as in western countries, the standard diagnostic imaging workup in centers performing MT within 6 hours since stroke onset closely matches the imaging techniques used in these clinical trials [5,6]. AdvImg, by allowing brain perfusion assessment, can more accurately assess the volumes of the infarct core and, above all, salvageable brain tissue (penumbra). It is, therefore, expected to better identify AIS patients with large vessel occlusion who will benefit from late MT in clinical practice. The accuracy of imaging differs across technologies or remains unknown for devices under development. In addition, evidence is limited regarding the proportion of patients who would benefit from late MT [7,8]. In fact, this proportion is influenced by the different inclusion criteria used in trials. Since the availability of AdvImg is expected to influence future care of AIS patients, the aim of this study was to explore the cost-effectiveness of 2 care pathways or strategies for patients presenting with a suspected stroke in the UK: (1) MT within and beyond 6 hours, up to 24 hours, based on AdvImg selection versus (2) MT only within 6 hours based on conventional imaging selection (ie, CT and CTA). We also assessed the impact of jointly varying the AdvImg accuracy and the prior probability for AIS patients to benefit from late MT.

4.2 METHODS

The authors declare that all supporting data are available within the article and its Data Supplement.

General Description of the Study Methodology

The formal steps of modeling were followed with conceptualizing, scoping, structuring, populating, analyzing, and addressing uncertainty [9,10]. A decision-analytic model was designed in Microsoft Excel to analyze and compare the cost-effectiveness of 2 care pathways for the population of suspected stroke patients: (1) allowing MT within and beyond 6 hours, up to 24 hours, from symptom onset based on AdvImg selection versus (2) MT only within 6 hours from onset and based on conventional imaging selection with CT and CTA. The first care pathway will be referred to as AdvImg with early and late MT (AIELMT), whereas the second one will be referred to as CT-CTA with early MT (CCEMT). We also assessed the impact of jointly varying the AdvImg accuracy and the prior probability for AIS patients to benefit from late MT. The CCEMT pathway represented the standard UK pathway of the past few years: suspected stroke patients receive a CT and CTA systematically precedes MT. AIS patients whose onset is beyond 6 hours or unknown after CT assessment (ie, not receiving MT) will not receive CTA. The remainder of the AIS patients not receiving MT may, or not, have been assessed by CTA. The 2 care pathways were compared based on their respective diagnostic and subsequent treatment options. In addition to the treatments that were explicitly modeled (IV-tPA [intravenous tissue-type plasminogen activator] and MT), we assumed that patients received standard medical care (including antiplatelet therapy, blood pressure management, complication prevention, and rehabilitation).

A hypothetical UK cohort of suspected stroke patients aged 71 years with a first-ever stroke was modeled. A literature search was performed to populate the input parameters, and clinical experts were consulted to ascertain some of them. Using 2 time-horizons of, respectively, 3 months and lifetime, costs, quality-adjusted life years (QALYs), and life years (LY) were calculated for each care pathway. Costs and effects were discounted at 3.5%. The perspective was the UK NHS which did not include societal costs. No ethics approval was needed.

Model structure

Decision Tree

A short-run decision tree model (Figure 4.1A) was built to predict the costs and clinical outcomes at 90 days after the first suspected stroke. A hypothetical cohort of initially independent patients (ie, with a modified Rankin Scale [mRS] of 0–2) was distributed at 90 days into 1 of 4 possible subgroups, as follows: recovered (mRS 0), independent (mRS 1 or 2), dependent (mRS 3, 4, or 5) and dead (mRS 6). Treatment effects were assumed to occur during the acute phase. From the initial cohort of suspected stroke patients, hemorrhagic stroke patients, and nonstroke patients (tumors, other conditions) were

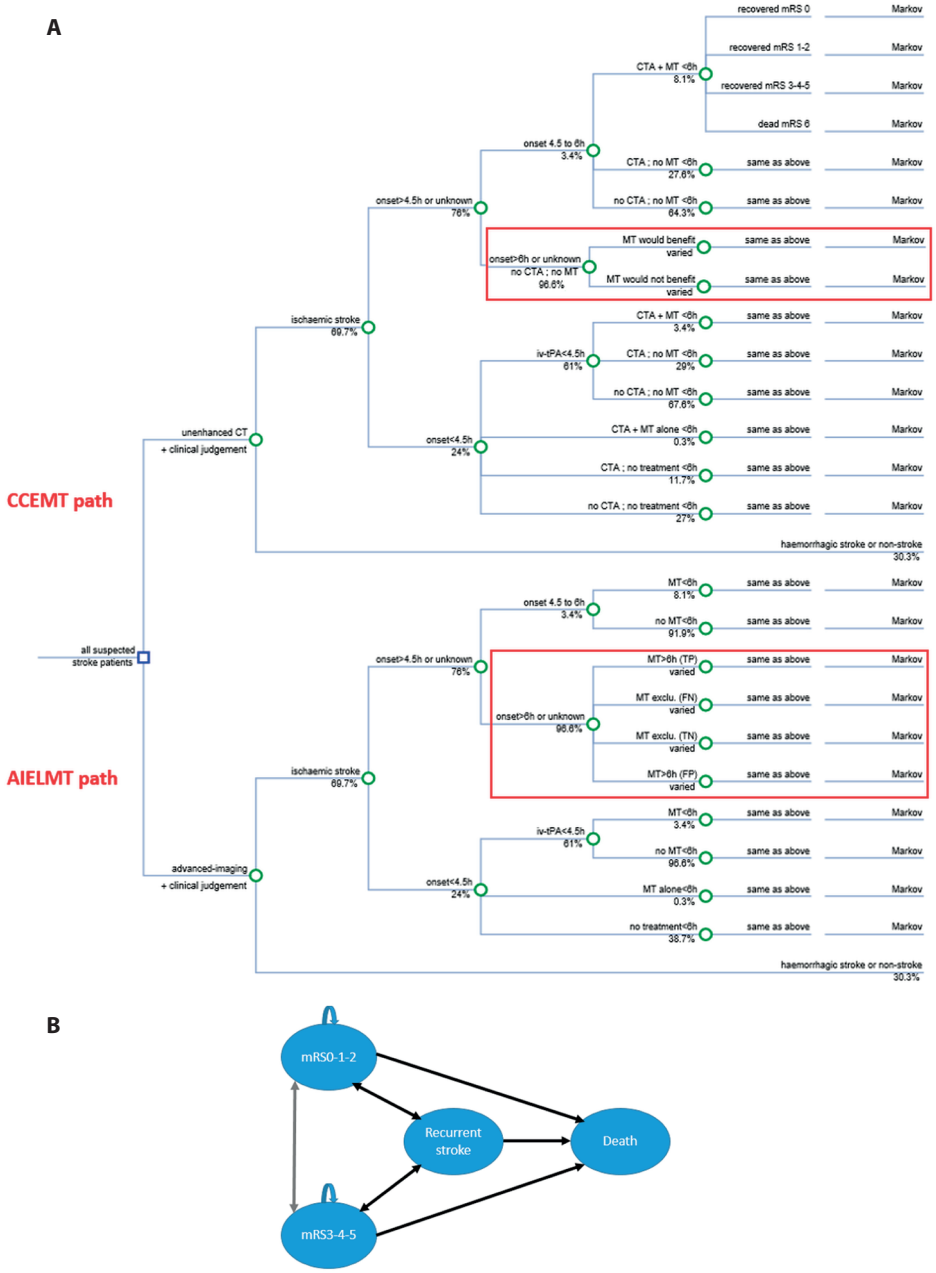
assumed to have the same health outcomes in the CCEMT strategy as in the AIELMT strategy and were, therefore, not modeled in detail. Furthermore, we assumed that AdvImg performs as good as unenhanced CT in diagnosing hemorrhagic strokes and equal or better than CT+CTA in identifying nonstrokes. Clinical judgment was assumed to complement CT and AdvImg. The probabilities for a patient to end up in each group (ie, recovered [mRS 0], independent [mRS 1 or 2], dependent [mRS 3, 4, or 5], or dead [mRS 6]) at 90 days were calculated using data provided by trials and registries. We applied the probabilities reported in Table I in the Data Supplement.

Markov Model

Data from the short-run model related to AIS patients fed into a long-run Markov state-transition model (Figure 4.1B) built to predict, from initial diagnosis, the lifetime costs, and outcomes. The model was based on 3-month cycles and ran until all patients died to reflect a lifetime time horizon (150 cycles appeared adequate for this purpose). Given the data available, patients in mRS 0 and mRS 1–2 were grouped together in mRS 0–2 in the Markov model. It was assumed that patients in mRS 0–2 and mRS 3–5 could move between these states only during the first year, due to deterioration or rehabilitation. Patients experiencing a recurrent stroke could either maintain the status they were in before recurrence or deteriorate. Previous studies indicated that dependent patients (mRS 3–5) have increased mortality compared to independent patients (mRS 0–2) [11,12]. We used a 1.29 hazard ratio for mRS 0–2 and a 3.33 hazard ratio for mRS 3–5 compared with UK population averages (see Table II in the Data Supplement). We used UK life tables for age- and sex-adjusted all-cause mortality rates applying from year 2 onwards. As the life table data from the UK were truncated at 100 years, the mortality starting at 101 years was kept constant and equal to the mortality at 100 years.

Patients experiencing a recurrent stroke were managed based on the same strategy as during their initial stroke. If an independent patient experienced a recurrent stroke, the probabilities of remaining in mRS 0–2, moving to mRS 3–5, or dying were the same as the probabilities after the initial stroke. However, a dependent patient experiencing recurrent stroke could only remain in the dependent state or die. Furthermore, the probability of an individual in the dependent state to die from recurrent stroke was assumed to be the same as that of an independent patient experiencing recurrent stroke. Based on previous studies, the risk of recurrence was assumed to be equal for mRS 0–2 and mRS 3–5 [13,14]. A maximum of 1 recurrent stroke per patient per 3-month cycle was assumed. The transition probabilities can be found in Table I in the Data Supplement.

Figure 4.1 Structure of the decision tree model and Markov model. A, Decision tree model representing the diagnostic, acute treatment and outcomes at 90 d after initial stroke. B, Markov model reflecting long-term expectations for post-initial stroke patients.



AdvImg indicates advanced imaging; AIELMT, AdvImg with early and late MT; CCEMT, CT-CTA with early MT; CT, computed tomography; CTA, CT angiography; FN, false negative; FP, false positive; IV-tPA, intravenous tissue-type plasminogen activator; mRS, modified Rankin Scale; MT, mechanical thrombectomy; TN, true negative; and TP, true positive.

Modeling AdvImg Accuracy in the AIELMT Strategy

Late MT after 6 hours from onset was only possible if it was indicated by AdvImg; therefore, only patients in the AIELMT strategy could undergo late MT. The choice was made to model late MT for AIS patients who did not receive IV-tPA previously (see Figure 4.1A). In the decision tree, the value of similar input parameters in the 2 strategies was kept equal, except for parameters related to MT beyond 6 hours. As such, AdvImg was assumed to have the same accuracy as CT+CTA to refer patients to MT until 6 hours from onset, and the model was structured to investigate the difference in effects and costs driven by performing late MT (AIELMT path) versus no late MT (CCEMT path). For this reason, the uncertainty regarding the benefits of MT was explicitly modeled only after 6 hours from onset. The accuracy of AdvImg beyond 6 hours was varied (see section about simulated scenarios). Health outcomes of late MT at 90 days (AIELMT strategy) were stratified according to the ability of AdvImg to correctly identify AIS patients for late MT. Outcomes were simulated for true positive, false positive, false negative, and true negative patients (Table III in the Data Supplement). Outcomes for false positive patients were based on the outcomes for true negative patients but corrected for the risk of procedural complications [15]. It was assumed that all false positive AIS patients, irrespective of the stroke severity, had an equal mortality risk due to complications (see Table IVa and IVb in the Data Supplement).

Costs and Resource Use

All costs were calculated in British pounds (£) for the year 2018 and presented in US$ using an exchange rate of £1=US$1.33. Costs originating from previous years were inflated based upon the pay and price index for Hospital and Community Health Services for 2017 [16]. The inflation factor from 2016 to 2017 (1.018) was used to inflate costs to 2018. Costs and resource used in the model are presented in Table I in the Data Supplement. The imaging cost of identifying the nonischemic stroke patients (nonstroke and hemorrhage) was computed to account for the cost difference between the diagnosis by CT-CTA and AdvImg (Figure 4.1A). The cost of IV-tPA consists of drug acquisition and drug administration. Details about the calculations can be found in Table Va and Vb in the Data Supplement. Based on clinical expert review, the cost of MT was sourced from a microcosting study and inflated to 2018 [14]. The mean acute costs incurred during the first 90 days after AIS and the mean 3-monthly long-term healthcare costs were found to be specific to the severity of the outcome (mRS) in the literature. These costs included nurse visits, general practitioner visits, emergency care, outpatient visits, day cases, and hospitalizations. CT costs were deducted from the costs of the first 3 months since the found estimates already included initial diagnostic tests for a suspected stroke. The cost of a recurrent stroke, including the cost of the 3 following months, was based upon the findings of the short-run model and was assumed to be specific to either the CCEMT

strategy or AIELMT strategy. Therefore, it represents the deterministic estimate of the cost to identify and treat an average ischemic stroke according to the care pathways defined in the decision tree. Costs incurred in the future were assumed to be similar to those incurred in the present and the first 3 months following a recurrent stroke to be equally costly as the 90 days following the initial stroke.

Utilities/Quality of Life

Utilities were assigned to each of the 3 possible health states of the mRS based on a study by Wardlaw et al who performed a review of utilities used in previous economic evaluations [17]. Utility values ranged from 0.71 for mRS 0–2 to 0.20 for mRS 3–5 to 0 for mRS 6. The utility of a recurrent ischemic stroke was derived from the short-run model and, therefore, assumed to be specific to the CCEMT strategy and AIELMT strategy. Utilities were varied according to a beta distribution (see Table I in the Data Supplement).

Simulated Scenarios

In line with the principles of economic evaluations of diagnostic technologies, we ran scenario analyses on 2 important parameters, test accuracy, and prior probability to benefit from late MT, to assess their impact on the cost-effectiveness of the AIELMT strategy. Because evidence regarding the effectiveness of late MT is lacking due to the experimental nature of the indication, we simulated different proportions of patients potentially benefitting from an intervention beyond 6 hours from onset. As such, 3 scenarios were simulated in which the prior probability of benefitting from MT (before AdvImg information is obtained) was varied from 10% to 20% and 30% (Table). The prior probability was defined as the probability for an AIS patient imaged beyond 6 hours after onset to benefit from late MT. In the CCEMT path, patients with an onset above 6 hours (therefore not receiving MT) were split between those who would theoretically benefit from late MT and those who would not, based on the prior probability. Patients in the AIELMT strategy were, in theory, referred to late MT according to the AdvImg preprocedural findings. CT perfusion is the most commonly used AdvImg technique in the diagnosis of AIS patients. Its accuracy was reported mainly when image acquisition occurred within the 6-hour window from onset with a mean sensitivity of 80% and a mean specificity of 95% [18]. We assumed that the sensitivity of AdvImg beyond 6 hours would not go below the sensitivity reported for testing within 6 hours and used 80% as the minimal value in our scenario analysis. Specificity was tested for its impact on the cost-effectiveness results and was set to a minimum value of 70%. Therefore, we simulated a perfect AdvImg test (sensitivity=specificity=100%), a test with reduced sensitivity to 80% (and 100% specificity) and a test with reduced specificity to 70% (and 100% sensitivity). The probability to be referred to late MT based on AdvImg, therefore,

varied according to 9 scenarios based on the pairwise combination of prior probability and accuracy of imaging (Table 4.1).

Table 4.1 Parameters for the 9 scenario analyses based on pairwise variation of prior probability and AdvImg accuracy

Set of parameters for the 9 scenario analysis	Prior probability = 30%	Prior probability = 20%	Prior probability = 10%
Perfect AdvImg test	Scenario 1 TP=0.3 FN=0 FP=0 TN=0.7	Scenario 2 TP=0.2 FN=0 FP=0 TN=0.8	Scenario 3 TP=0.1 FN=0 FP=0 TN=0.9
AdvImg test with a sensitivity of 80% and a specificity of 100%	Scenario 4 TP=0.24 FN=0.06 FP=0 TN=0.7	Scenario 5 TP=0.16 FN=0.04 FP=0 TN=0.8	Scenario 6 TP=0.08 FN=0.02 FP=0 TN=0.9
AdvImg test with a sensitivity of 100% and a specificity of 70%	Scenario 7 TP=0.3 FN=0 FP=0.21 TN=0.49	Scenario 8 TP=0.2 FN=0 FP=0.24 TN=0.56	Scenario 9 TP=0.1 FN=0 FP=0.27 TN=0.63

AdvImg indicates advanced imaging; FN, false negative; FP, false positive; TN, true negative; and TP, true positive.

Sensitivity Analysis

A probabilistic sensitivity analysis (PSA) was performed to assess the impact of the uncertainty around the input parameter values. This was implemented by assigning a distribution to each parameter to represent the uncertainty around its mean value. A random value was sampled from each distribution, and the results were calculated using the set of sampled values. This process was repeated in 3000 simulations per scenario to generate 3000 estimates of the costs, QALYs, and LY in each scenario of each strategy. This number of simulations matched the number needed to obtain stable estimates. The proportion of simulations when the AIELMT path had the highest net monetary benefit was calculated for a range of values of the willingness to pay for a QALY. The results were presented with cost-effectiveness acceptability curves. Each curve represented the probability that the AIELMT strategy was cost-effective compared with the CCEMT strategy at different thresholds for cost-effectiveness.

4.3 RESULTS

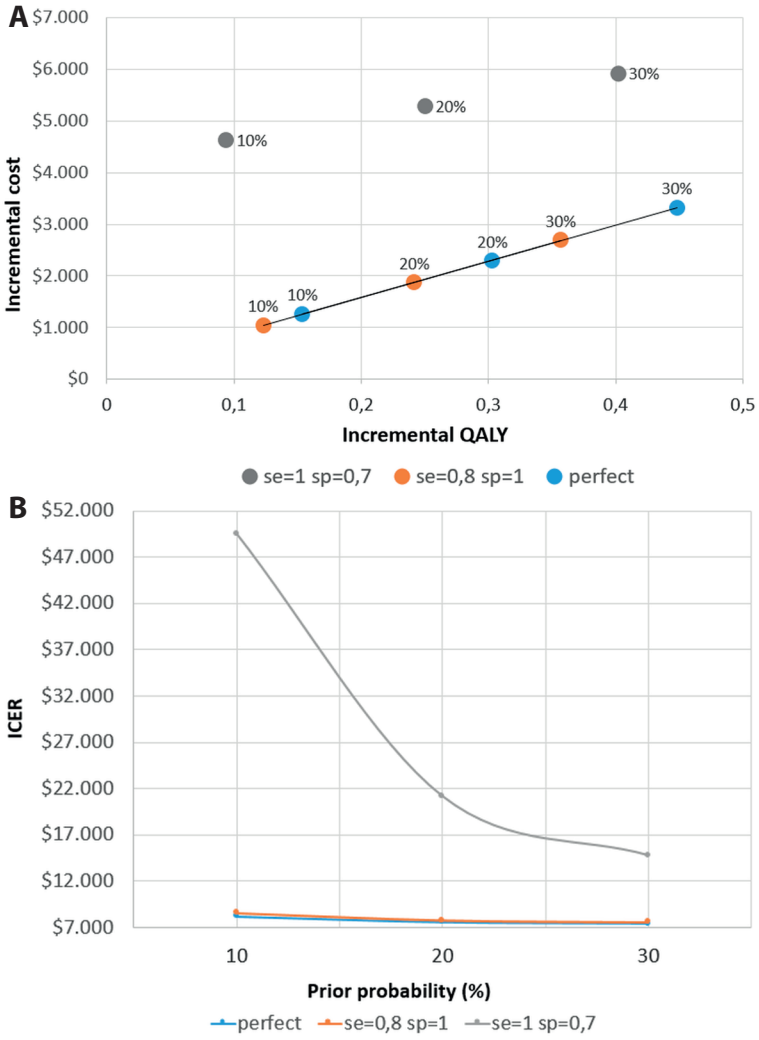
At 90 days after the initial AIS, most AIELMT scenarios (1, 2, 3, 4, 5, 6, 7, and 8) increased the proportions of fully recovered patients, decreased mortality, and generally improved outcomes on the mRS scale, compared with the CCEMT strategy. Scenario 9 (sensitivity 100%; specificity 70%) increased mortality (because of MT-related mortality risk in false positive patients) at 90 days but still increased QALYs. The distribution of AIS patients across the mRS scale at 90 days was used as the starting point in the Markov model and can be found in Table VI in the Data Supplement.

At lifetime horizon, in the 9 scenarios, the AIELMT strategy was associated with a health gain, ranging from 0.09 to 0.45 QALYs, per AIS patient. It was also associated with a higher cost per AIS patient, ranging from $1051 (£790) to $5932 (£4460) (Table VII in the Data Supplement). QALYs and LYs are higher in the AIELMT path as this strategy saves lives and improves health outcomes on the mRS scale compared with the CCEMT strategy. The incremental long-term costs were induced by the cost of MT and the longer survival of patients in the AIELMT strategy. A higher prior probability of benefitting from late MT led to higher additional costs and more QALYs in the AIELMT strategy.

Based on a lifetime horizon, there is a similar linear relationship between the incremental costs and incremental QALYs in the 6 scenarios of the perfect test and the reduced sensitivity test (Figure 4.2A). Although incremental costs and incremental QALYs increase as the prior probability increases, the incremental cost-effectiveness ratios (at different prior probabilities) for the perfect test and the reduced sensitivity test remain almost equal. In the reduced specificity scenario, when increasing the prior probability, incremental effects are increasing faster than incremental costs, which results in a lower lifetime incremental cost-effectiveness ratio (cost per QALY gained) as the prior probability rises ($49 515 [£37 229] at 10%, $21 156 [£15 906] at 20%, and $14 765 [£11 101] at 30%; Figure 4.2B). In the reduced specificity scenario, when the prior probability increases, smaller impacts are observed on costs, as the frequency of false positive goes down. Details about the incremental cost-effectiveness ratios at 90 days and lifetime related to both the LYs and QALYs can be found in Table VIII in the Data Supplement.

Probabilistic sensitivity analyses confirmed that the higher the prior probability, the higher the cost difference and the effect difference between the 2 care pathways, with increased costs and effects observed in the AIELMT strategy (Figure 4.3A). Furthermore, at a constant prior probability, the cost difference increased in the case of the decreased specificity test but stayed quasisimilar for both the perfect and decreased sensitivity test (Figure 4.3B).

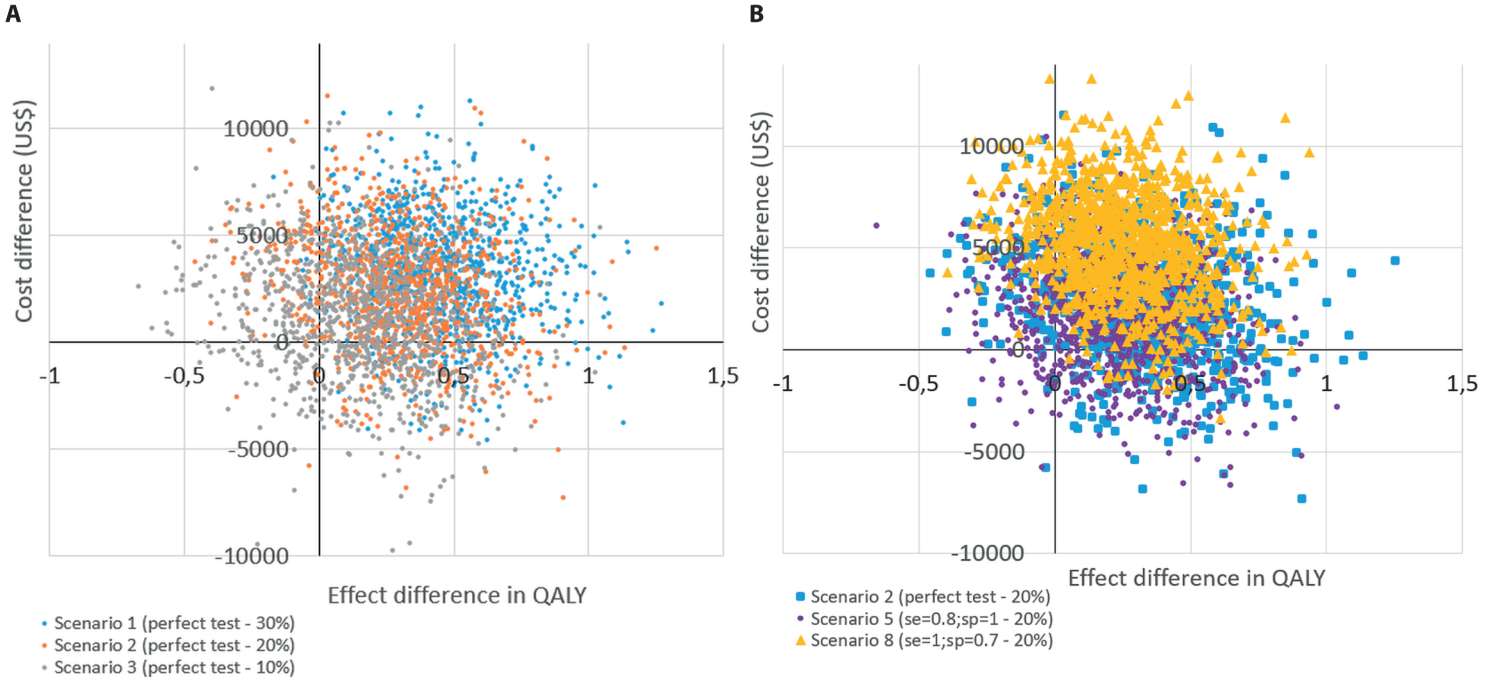
Figure 4.2 Lifetime results for the 9 scenarios. A, Cost and quality-adjusted life year (QALY) differences between computed tomography (CT)–CT angiography with early mechanical thrombectomy (CCEMT) and advanced imaging with early and late MT (AIELMT) strategy for the 9 scenarios. % refers to the prior probability to benefit from late MT. B, Incremental cost-effectiveness ratio (ICER) at lifetime time horizon for different levels of advanced imaging accuracy.

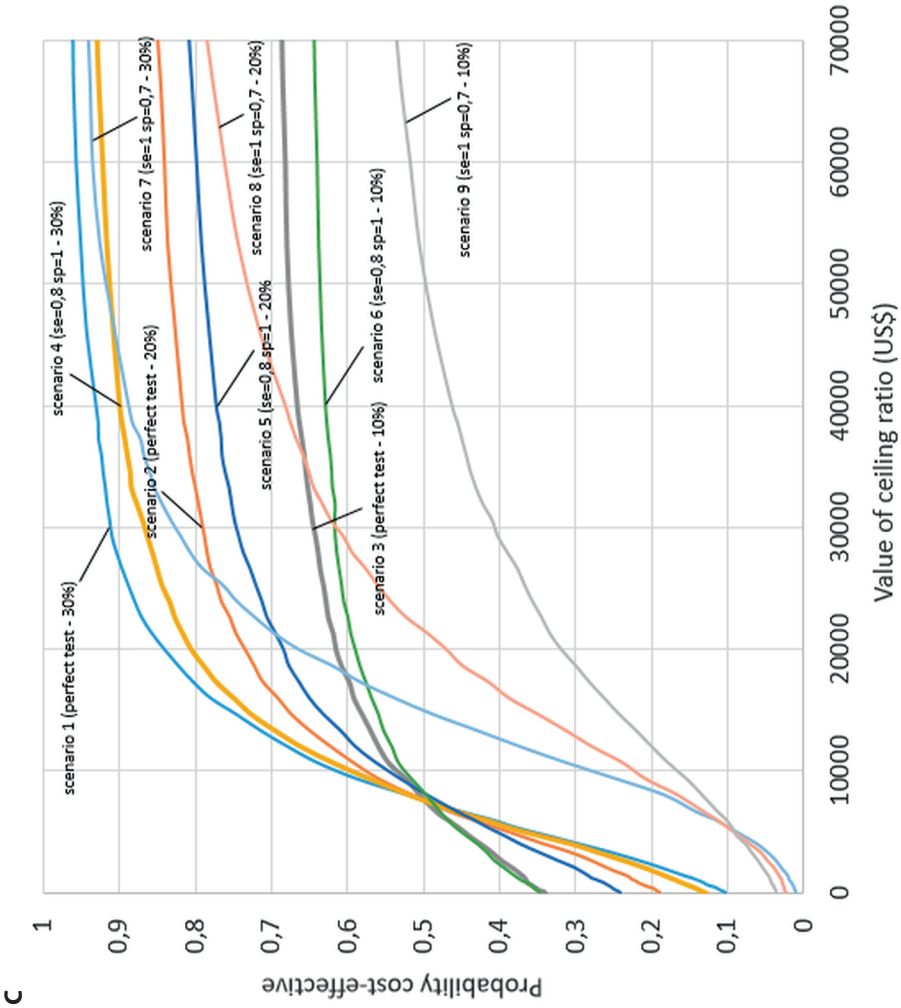


Se indicates sensitivity; and Sp, specificity.

The cost-effectiveness acceptability curves for the AIELMT strategy show that, at a willingness to pay of $39 900 (£30 000), the probability of being cost-effective was above 46% in the 9 scenarios (Figure 4.3C). With reduced specificity, the probability of the AIELMT strategy to be cost-effective at low willingness to pay thresholds dropped substantially.

Figure 4.3 Results of the probabilistic sensitivity analyses.
A, Monte Carlo simulations of incremental cost per quality-adjusted life year (QALY) gained of advanced imaging with early and late mechanical thrombectomy (AIELMT) in 3 scenarios of perfect test and different prior probability.
B, Monte Carlo simulations of incremental cost per QALY gained of AIELMT in 3 scenarios of a 20% prior probability and different imaging accuracy.
C, Cost-effectiveness acceptability curves showing the probability that the AIELMT pathway is cost-effective at different values of willingness to pay for a QALY, for the 9 scenarios compared to the computed tomography (CT)–CT angiography with early mechanical thrombectomy (CCEMT) pathway (CCEMT pathway curves not shown).




C
Probability cost-effective
1
0,9
0,8
0,7
0,6
0,5
0,4
0,3
0,2
0,1
0
0
10000
20000
30000
40000
50000
60000
70000
Value of ceiling ratio (US$)
scenario 1 (perfect test - 30%)
scenario 2 (perfect test - 20%)
scenario 3 (perfect test - 10%)
scenario 4 (se=0,8 sp=1 - 30%)
scenario 5 (se=0,8 sp=1 - 20%
scenario 6 (se=0,8 sp=1 - 10%)
scenario 7 (se=1 sp=0,7 - 30%)
scenario 8 (se=1 sp=0,7 - 20%)
scenario 9 (se=1 sp=0,7 - 10%)

4.4 DISCUSSION

Our main finding is that AdvImg, by extending the time window beyond 6 hours (up to 24 hours) for MT, improves health outcomes but increases costs when compared with conventional imaging (CT+CTA) coupled to MT up to only 6 hours from symptom onset. Incremental cost-effectiveness ratios resulting from our deterministic analyses varied from $8199 (£6164) to $49 515 (£37 229) per QALY gained. This study suggests that late MT based on AdvImg selection is cost-effective in the UK. However, at a willingness to pay threshold of $39 900 (£30 000), the probability of an AIELMT strategy to be cost-effective varies widely across scenarios.

Since the evidence regarding the probability to benefit from late MT based on AdvImg criteria is limited, extensive scenario and uncertainty analyses were performed. These analyses showed that reduced specificity of AdvImg reduces the cost-effectiveness. However, the magnitude of this impact decreases as the prior probability for AIS patients to benefit from late MT increases. These findings suggest that advanced neuroimaging should focus on excluding patients without sufficient salvageable tissue to avoid unnecessary interventions and make the benefit of (late) MT worth the considerable resource utilization.

Compared with previous economic studies that assessed the value of MT after IV-tPA versus IV-tPA alone, our study presents comprehensive results about the cost-effectiveness of an integrative UK care pathway that combines AdvImg and all possible subsequent early and late acute treatments [14,19,20,21]. Despite methodological differences, our results on the value of late MT are consistent with the results published by Pizzo et al. who demonstrated that MT performed between 6 and 24 hours after onset is cost-effective in the UK [19]. To the best of our knowledge, our study is the first to explore the combined impact of uncertainty from imaging accuracy and prior probability on the cost-effectiveness of late MT.

Our results may have important policy implications. Commissioning criteria for late MT by NHS England are based on the identification of substantial salvageable brain tissue up to 12 hours after onset by perfusion or multiphase CTA [3]. Strong evidence about the accuracy of these imaging techniques for late MT referral is crucial to ascertain whether the NHS policy commissions a cost-effective practice. As shown above, a decreased specificity might considerably lower the probability for an AIELMT strategy to be cost-effective. Strong evidence also implies the assessment of technology-specific preprocedural findings in terms of their ability to predict clinical outcomes. Quantification of the amount of salvageable brain tissue required before neurointervention and definition

of the target in terms of clinical outcomes per patient might be needed to clarify the commissioning policy. Once this is clear, the AIELMT pathway may be implemented.

Implementation of the AIELMT pathway will have considerable consequences for the NHS in terms of number of patients treated and costs. From April 2016 to March 2017, 85 122 cases of strokes were reported in the UK, Wales, and Northern Ireland [22]. Assuming that 85% of those were ischemic, we estimated about 72 350 AIS patients [3]. According to the probabilities used in our model, 76% of these patients (about 55 000) were imaged beyond 4.5 hours, and 97% of the latter (about 53 350) were imaged beyond 6 hours from onset. Applying a prior probability of 20%, a decreased sensitivity of 80%, and a perfect specificity, about 8500 of these patients would receive MT, should the infrastructure and manpower allow this capacity. Compared with data on recent care (2016–2017), in which 580 MT were performed, the incremental budget impact of performing AdvImg and late MT would be around $93 (£70) million [22].

However, providing widely accessible AdvImg is likely to be an organizational challenge for the NHS, for 2 reasons. First, AdvImg would probably be available only at comprehensive stroke centers. Assuming that around 25% of stroke patients would be directly attending a comprehensive center (providing MT) and 75% first attending a local acute stroke unit (providing IV-tPA only), a major question arises on how to handle the stroke patients at local units providing only CT and CTA and whether to transfer them to a comprehensive center [23]. Second, there is currently no emergency transfer infrastructure supporting a system based on widely accessible AdvImg and MT. So, probably more realistically, only those directly attending a comprehensive stroke center will have access to AdvImg and late MT. This illustrates the challenge of embedding new technologies in the existing healthcare system and the need for the organization of stroke care to evolve. In that respect, the optimal ratio of comprehensive stroke centers versus local acute stroke units should be determined.

We acknowledge limitations in our study. First, our model combines treatment outcomes per time since onset from different studies investigating slightly different AIS populations. Given the model structure, it was impossible to use inputs based on one single comprehensive source of treatment outcomes. To overcome this limitation, comprehensive real-world data are needed, especially regarding the first 3 months after AIS onset. However, since this limitation influences equally, the 2 strategies of our comparison, the incremental results of our model are not affected. More importantly, the outcomes of the DAWN trial (Diffusion Weighted Imaging or Computerized Tomography Perfusion Assessment With Clinical Mismatch in the Triage of Wake Up and Late Presenting Strokes Undergoing Neurointervention With Trevo) were used, that included

5% of patients who received IV-tPA in the intervention arm and 13% in the control arm. This contrast slightly influences our incremental results by underestimating the value of the AIELMT pathway. Second, we conservatively assumed no difference between the AdvImg and CT-CTA strategies regarding the ability to detect stroke mimics. Inclusion of an improved ability by AdvImg to detect stroke mimics would have resulted in a more favorable estimated cost-effectiveness. Third, although we used the best available cost data for generalizability, these were based on a patient population presenting with a history of atrial fibrillation [24].

We explored the value of AdvImg for late MT. Beyond our investigation, crucial research questions remain to assess the comprehensive value of AdvImg and how it could improve the early stroke care pathway. First, with a single image acquisition, AdvImg might save time and diagnose more patients within the 4.5- and 6-hour window, compared with CT+CTA and, in turn, refer more patients to treatment. Second, AdvImg might offer increased accuracy within the 6-hour window compared with the currently used imaging techniques. Since the accuracy of AdvImg in AIS is specific to the lesion type and size, to the location of the lesion in the brain, and to the time since onset, assessing the full value of AdvImg along the stroke care pathway is challenging. Third, further clinical research regarding the percentage of patients likely to benefit from late MT is needed to optimize the stroke care pathway in the UK.

Finally, although US dollar equivalents are provided, this analysis does not reflect the US healthcare costs and is not generalizable to the US healthcare setting. Although diagnostic and treatment guidelines for AIS patients are similar in the Unites States and the UK, the reported mean lifetime cost of AIS is $140 000 in the United States, which is 2.33× our UK estimate [25]. Based on exploratory analyses, the remuneration of physicians and the cost of hospitalization and IV-tPA are the main contributors to the cost difference (data not shown). These observations suggest that AdvImg and late MT would be more cost-effective in the United States than in the UK.

4.5 CONCLUSIONS

Based on these exploratory results, referring AIS patients to MT beyond the 6-hour window by means of AdvImg may be good value for money in the UK. However, additional data regarding the prior probability to benefit from late MT and the accuracy of imaging for AIS patients is needed before MT can be widely implemented in clinical practice.

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Table I. Model parameters and range of values for sensitivity analysis

Probabilities in the decision tree				
Model input Probability that/of	Base-case value	Distribution	Distribution parameters	Reference(s) and comments
a suspected stroke patient of the emergency setting has an ischemic stroke	69.7%	Dirichlet	0-1	SSNAP Sentinel Stroke National Audit Programme [1]
a suspected stroke patient of the emergency setting has an hemorrhagic stroke	10.2%	Dirichlet	0-1	
a suspected stroke patient of the emergency setting has a non-stroke	20.1%	Dirichlet	0-1	Watkins [2]
an ischemic patient is imaged (CT or AdvImg) within 4.5 hours after symptom onset	24%	Beta	$\alpha = 24$ $\beta = 76$ *	Multiple sources, see calculation methods in Appendix
an ischemic patient is imaged (CT or AdvImg) beyond 4.5 hours or that the time from symptom onset is unknown	76%	Beta	NA*	
an ischemic patient imaged (CT or AdvImg) beyond 4.5 hours is assessed within 6 hours after symptom onset	3.4%	Beta	$\alpha = 3$ $\beta = 97$ *	Multiple sources, see calculation methods in Appendix
an ischemic patient imaged (CT+CTA or AdvImg) between 4.5 and 6 hours receives MT within 6 hours	8.1%	Dirichlet	0-1	Multiple sources, see calculation methods in Appendix
an ischemic patient fully imaged (CT+CTA) between 4.5 and 6 hours does not receive MT within 6 hours	27.6%	Dirichlet		CCEMT strategy: 30% of the patients imaged between 4.5 and 6 hours and not receiving MT were assumed to have received a CTA
an ischemic patient imaged (CT) between 4.5 and 6 hours receives neither CTA nor MT within 6 hours	64.3%	Dirichlet		

Table I. Model parameters and range of values for sensitivity analysis (*continued*)

Probabilities in the decision tree					
an ischemic patient who received IV-tPA receives MT (following CTA for the CCEMT path) within 6 hours	3.4%	Dirichlet	0-1	Multiple sources, see calculation methods in Appendix.	
an ischemic patient who received IV-tPA receives CTA but no MT within 6 hours	29%	Dirichlet		CCEMT strategy: 30% of the patients who received IV-tPA and are not receiving MT were assumed to have received a CTA	
an ischemic patient who received IV-tPA receives neither CTA nor MT within 6 hours	67.6%	Dirichlet			
an ischemic patient imaged (CT or AdvImg) within 4.5 hours receives IV-tPA	61%	Dirichlet	0-1	SSNAP Sentinel Stroke National Audit Programme [1] See calculation in Appendix	
an ischemic patient imaged (CT or AdvImg) within 4.5 hours receives MT alone (without IV-tPA) (following CTA for the CCEMT path) within 4.5 hours	0.3%	Dirichlet		Multiple sources, see calculation methods in Appendix	
an ischemic patient imaged within 4.5 hours receives CTA but no treatment within 4.5 hours (CCEMT strategy)	11.7%	Dirichlet		CCEMT strategy: 30% of the patients who did not receive IV-tPA and are not receiving MT were assumed to have received a CTA	
an ischemic patient imaged (CT or AdvImg) within 4.5 hours receives no CTA and no treatment within 4.5 hours (CCEMT strategy)	27%	Dirichlet			
*: given the different sources used and hypothesis made in calculating the base-case value, we considered a conservative sample size of 100 to calculate the α and β					
Health outcomes at 90 days in the decision tree			**Range**		**Comments**
mRS 0 after MT beyond 4,5 and up to 6 hours from onset	7.9%	Dirichlet	0-1	Minnerup [3]	Germany, REVASK registry
mRS 1-2 after MT beyond 4,5 and up to 6 hours from onset	33.2%	Dirichlet	0-1		
mRS 3-5 after MT beyond 4,5 and up to 6 hours from onset	33.9%	Dirichlet	0-1		
mRS 6 after MT beyond 4,5 and up to 6 hours from onset	25%	Dirichlet	0-1		

Table I. Model parameters and range of values for sensitivity analysis (*continued*)

Probabilities in the decision tree					
mRS 0 after no IV-tPA nor MT beyond 4,5 and up to 6 hours from onset	18%	Dirichlet	0-1	Hacke [4]	14 European countries Australia and New-Zealand. ECASS II trial. Outcome for the placebo-group patients (against iv-TPA).
mRS 1-2 when no IV-tPA nor MT beyond 4,5 and up to 6 hours from onset	28.3%	Dirichlet	0-1		
mRS 3-5 when no IV-tPA nor MT beyond 4,5 and up to 6 hours from onset	43.5%	Dirichlet	0-1		
mRS 6 when no IV-tPA nor MT beyond 4,5 and up to 6 hours from onset	10.4%	Dirichlet	0-1		
Health outcomes for patients with onset above 6 hours					
TP (AIELMT strategy)					
mRS 0 after LVO and MT alone beyond 6 hours from onset	9.3%	Dirichlet	0-1	Nogueira [5]	DAWN trial, MT arm, 5% of the patients in the arm received IV-tPA
mRS 1-2 after LVO and MT alone beyond 6 hours from onset	39.3%	Dirichlet	0-1		
mRS 3-5 after LVO and MT alone beyond 6 hours from onset	26.3%	Dirichlet	0-1		
mRS 6 after LVO and MT alone beyond 6 hours from onset	25.3%	Dirichlet	0-1		
FN and MT would benefit (respectively AIELMT and CCEMT strategies)					
mRS 0 after LVO and no MT beyond 6 hours from onset	4.3%	Dirichlet	0-1	Nogueira [5]	DAWN trial, control arm, 13% of the patients in the arm received IV-tPA
mRS 1-2 after LVO and no MT beyond 6 hours from onset	9.3%	Dirichlet	0-1		
mRS 3-5 after LVO and no MT beyond 6 hours from onset	50.3%	Dirichlet	0-1		
mRS 6 after LVO and no MT beyond 6 hours from onset	36.3%	Dirichlet	0-1		

Table I. Model parameters and range of values for sensitivity analysis (*continued*)

Probabilities in the decision tree					
TN and MT would not benefit (respectively AIELMT and CCEMT strategies)					
mRS 0 after mild stroke and no MT beyond 6 hours from onset	18.3%	Dirichlet	0-1	Lees [6]	Pooled analysis from 9 randomized trials, patients with mild stroke (NIHSS 5 to 10, mean NIHSS 7.4, control arm against IV-tPA (supplementary material)
mRS 1-2 after mild stroke and no MT beyond 6 hours from onset	42.5%	Dirichlet	0-1		
mRS 3-5 after mild stroke and no MT beyond 6 hours from onset	30.2%	Dirichlet	0-1		
mRS 6 after mild stroke and no MT beyond 6 hours from onset	9%	Dirichlet	0-1		
FP (AIELMT strategy)					
mRS 0 after mild stroke and no MT beyond 6 hours from onset	16.5%	Dirichlet	0-1	Lees [6] and Gascou [7]	Outcomes after correction of TN for procedural complications
mRS 1-2 after mild stroke and no MT beyond 6 hours from onset	40.7%	Dirichlet	0-1		
mRS 3-5 after mild stroke and no MT beyond 6 hours from onset	28.4%	Dirichlet	0-1		
mRS 6 after mild stroke and no MT beyond 6 hours from onset	14.4%	Dirichlet	0-1		
Health outcomes (AIELMT and CCEMT strategies)					
mRS 0 after IV-tPA and MT within 4.5 hours from onset	3%	Dirichlet	0-1	Berkhemer [8]	Netherlands, MR CLEAN trial, IV-tPA and MT arm, iv-tPA until 4.5 hours but MT until 6 hours
mRS 1-2 after IV-tPA and MT within 4.5 hours from onset	30%	Dirichlet	0-1		
mRS 3-5 after IV-tPA and MT within 4.5 hours from onset	46%	Dirichlet	0-1		
mRS 6 after IV-tPA and MT within 4.5 hours from onset	21%	Dirichlet	0-1		
mRS 0 after IV-tPA alone within 4.5 hours from onset	6.25%	Dirichlet	0-1	Berkhemer [8]	Netherlands, MR CLEAN trial, IV-tPA and MT arm
mRS 1-2 after IV-tPA alone within 4.5 hours from onset	29.25%	Dirichlet	0-1		
mRS 3-5 after IV-tPA alone within 4.5 hours from onset	42.25%	Dirichlet	0-1		
mRS 6 after IV-tPA alone within 4.5 hours from onset	22.25%	Dirichlet	0-1		

Table I. Model parameters and range of values for sensitivity analysis (*continued*)

Probabilities in the decision tree					
mRS 0 after MT alone within 4.5 hours from onset	7.9%	Dirichlet	0-1	Minnerup [3]	Germany, REVASK registry
mRS 1-2 after MT alone within 4.5 hours from onset	33.2%	Dirichlet	0-1		
mRS 3-5 after MT alone within 4.5 hours from onset	33.9%	Dirichlet	0-1		
mRS 6 after MT alone within 4.5 hours from onset	25%	Dirichlet	0-1		
mRS 0 after no IV-tPA nor MT within 4.5 hours from onset	17.95%	Dirichlet	0-1	Hacke [4]	14 European countries Australia and New-Zealand. ECASS II trial. Outcome for the placebo-group patients (against IV-tPA).
mRS 1-2 after no IV-tPA nor MT within 4.5 hours from onset	28.3%	Dirichlet	0-1		
mRS 3-5 after no IV-tPA nor MT within 4.5 hours from onset	43.4%	Dirichlet	0-1		
mRS 6 after no IV-tPA nor MT within 4.5 hours from onset	10.35%	Dirichlet	0-1		

TP: true positive; FP: false positive; FN: false negative; TN: true negative; IV-tPA: intravenous tissue-type plasminogen activator
MT: mechanical thrombectomy

Table I. Model parameters and range of values for sensitivity analysis *(continued)*

Transition probabilities in the Markov model					
				State at end of cycle	
		mRS 0-2	mRS 3-5	recurrent stroke	mRS 6
State at start of cycle	**Year 1 (month 3 to 12)**				
	mRS 0-2	0.955*	0.024*	0.013*	0.008*
	Distribution			Dirichlet (range 0-1)	
	mRS 3-5	0.029*	0.919*	0.013*	0.039*
	Distribution			Dirichlet (range 0-1)	
	Year 2 and onward				
	mRS 0-2	Varied based on mortality risk	0 (assumed)	0.013	UK life table [9] + hazard ratio: 1.29 [10]
	Distribution	Based on mortality risk	NA	Beta (α = 1.3 ; β = 98.7)	Log-normal for hazard ratio (SE=0.22)
	mRS 3-5	0 (assumed)	Varied based on mortality risk	0.013	UK life table [9] + hazard ratio: 3.33 [10]
	Distribution	NA	Varied based on mortality risk	Beta (α = 1.3 ; β = 98.7)	Log-normal for hazard ratio (SE=0.75)

*Ganesalingam [11]

Table I. Model parameters and range of values for sensitivity analysis *(continued)*

Transition probabilities after recurrence (base-case ranges for the 9 scenarios according to the results of the short-run 90-day decision-tree)				
CCEMT strategy			**State after recurrence**	
State before recurrence		**mRS 0-2**	**mRS 3-5**	**mRS 6**
	mRS 0-2	0.45 to 0.52	0.35 to 0.38	0.13 to 0.17
	mRS 3-5	0 **	0.83 to 0.87	0.13 to 0.17***
AIELMT strategy				
State before recurrence		**mRS 0-2**	**mRS 3-5**	**mRS 6**
	mRS 0-2	0.51 to 0.54	0.32 to 0.34	0.12 to 0.16
	mRS 3-5	0 **	0.84 to 0.88	0.12 to 0.16***

Distributions: No independent distribution was defined for these probabilities. Probabilities are varying based on the 3000 PSA results (expected value of probabilities) of the decision tree.

** assumed according to natural evolution of stroke

*** assumed to be equal to the transition from recurrence to death of patients initially in mRS 0-2

Table I. Model parameters and range of values for sensitivity analysis *(continued)*

Costs and resource use				
Item	**Base-Case value**	**Distribution**	**Range**	**Source**
Costs and resource use in the decision tree				
CT scan	$117 (£88)	Beta Pert	$113-$121 (£85-£91)	(RD20A) in the 2017/2018 National Schedule of Reference Costs [12]
CTA scan	$141 (£106)	Beta Pert	$135-$146 (£102-£110)	(RD21A) in the 2017/2018 National Schedule of Reference Costs [12]
Advanced-Imaging scan	$213 (£160)	Beta Pert	$186-$239 (£140-£180)	Assumed
IV-tPA (acquisition + administration)	$2,318 (£1743)	Beta Pert	$2,088-$2,548 (£1,570-£1,916)	Multiple sources, see calculation methods in Appendix
MT (including stent, material and surgery)	$11,784 (£8860)	Beta Pert	$8,261-$15,320 (£6,212-£11,519)	Ganesalingam [11], clinical expert feedback
Acute first 3-month costs		Beta Pert		Luengo-Fernandez [13]
mRS 0-2	$5,095 (£3,831)		$2,100-$8,090 (£1,579-£6,083)	
mRS 3-5	$29.274 (£22,011)		$22,934-$35,613 (£17,244-£26,777)	
mRS 6	$4.570 (£3,436)		$2,530-$6,611 (£1,902-£4,971)	

Table I. Model parameters and range of values for sensitivity analysis *(continued)*

Costs and resource use in the Markov model				
3-monthly long-term healthcare costs (day 90 onwards)		Beta Pert		Luengo-Fernandez [13]
mRS 0-2	$818 (£615)		$479-1,158 (£360-£871)	
mRS 3-5	$1738 (£1,307)		$912-2564 (£686-£1,928)	
Cost of recurrent stroke (90 days following stroke recurrence)		No independent distribution was defined. Costs are varying based on the 3000 PSA results (expected value of costs) of the decision tree.		From short-run 90-day decision-tree
In the CCEMT strategy	$9,827 (£7,389) to $10,307 (£7,750)			
In the AIELMT strategy	$10,161 (£7,640) to $12,534 (£9,424)			
Utilities				
Independent mRS 0-1-2	0.71	Beta	0.7-0.72	Wardlaw, analysis of CLOTS [14]
Dependent mRS 3-4-5	0.20	Beta	0.19-0.21	
Dead mRS 6	0	-	-	-
Recurrent stroke (90 days following stroke recurrence)		No independent distribution was defined. Utilities are varying based on the 3000 PSA results (expected value of stroke recurrence) of the decision tree.		From short-run 90-day decision-tree
In the CCEMT strategy	0.28 to 0.31			
In the AIELMT strategy	0.30 to 0.32			

Table II. Hazard ratios for mortality
Table from Slot et al. study [10]**.**

mRS	Lothian (N=2054)
0	1; N=283
1	0.98 (0.63, 1.54); N=404
2	1.74 (1.16, 2.61); N=455
3	2.58 (1.73, 3.87); N=360
4	3.89 (2.48, 6.12); N=122
5	4.98 (3.15, 7.88); N=122
6	0

A weighted average of these values gives 1.29 for mRS012 and 3.33 for mRS345.

Table III. Intermediate outcomes of late MT according to advanced imaging accuracy (as modelled in the AIELMT strategy of the decision tree)

	Truth (late MT will be beneficial)	**Truth (late MT will not be beneficial)**
Positive test (AdvImg informs that late MT will be beneficial)	**TP rate** (patients with LAO moderate or severe receiving late MT) = prior probability * sensitivity	**FP rate** (patients with LAO mild or small occlusions receiving late MT) = 1 – TP – FN – TN
Negative test (AdvImg informs that late MT will not be beneficial)	**FN rate** (patients with LAO moderate or severe not receiving late MT) = prior probability - TP	**TN rate** (patients with LAO mild or small occlusions not receiving late MT) = (1 – prior probability) * specificity
	Sensitivity = TP/(TP+FN)	**Specificity = TN/(FP+TN)**

TP: true positive; FP: false positive; FN: false negative; TN: true negative
MT: mechanical thrombectomy

Table IV. Outcomes for FP AIS patients after correction for embolic and hemorrhagic complications after standalone MT (AIELMT strategy)

a) Rates of periprocedural complications and deaths after complications after MT

	Standalone MT	**MT combined to IV-tPA**	**Death after complications**	**Death after embolic and hemorrhagic complications after standalone MT**
Total patients	50	94	-	
Embolic complications	8 (16%)	10 (10.6%)	38.9%	16% * 38.9% = 6.2%
Hemorrhagic complications	9 (18%)	20 (21.3%)	45.5%	45.5% * 18% = 8.2%
				6.22% + 8.19% = 14.4%

b) Outcomes for FP AIS patients after correction for periprocedural complications

	Outcome for TN (no MT)	**Outcome for FP (MT) in the AIELMT strategy after correction for complications after MT**
mRS 0 after mild stroke and beyond 6 hours from onset	18.3%	16.5%
mRS 1-2 after mild stroke and beyond 6 hours from onset	42.5%	40.7%
mRS 3-5 after mild stroke and beyond 6 hours from onset	30.2%	28.4%
mRS 6 after mild stroke and beyond 6 hours from onset	9%	**14.4%**

Table Va. Inflated 2016/17 resource use costs for administration of IV-tPA from Sandercock et al. [15]

Extra staffing requirements	Comments	PSSRU 2017 definitions	2016/2017 cost per hour	2018 inflated cost per hour	2018 cost
5 min additional nurse time	PSSRU 2011 (staff nurse 24hr ward)	Nurse (Band 5) (Section 14 of PSSRU 2017) Cost per hour of patient contact	£89 (Cost per working hour is £37)	£90.59	£7.55
190 min registrar time	PSSRU 2011 (registrar group)	Registrar (Section 15 of PSSRU 2017). Cost per working hour	£43	£43.77	£138.60
50 min consultant time	PSSRU 2011 (medical consultant costs)	Medical consultant (Section 15 of PSSRU 2017) Cost per working hour	£106	£107.89	£89.91
5 min routine observation by senior nurse in place of more junior nurse	It has been assumed that observations are carried out by a senior nurse, and that each observation takes 5 minutes PSSRU 2011 (ward manager 24hr ward and staff nurse 24hr ward)	Nurse advanced (band 7) (Section 14 of PSSRU 2017) Cost per hour of patient contact	£131 (Cost per working hour is £54)	£133.34	£11.11
12 additional sets of observations at 5 min each	It has been assumed that routine observations take 5 minutes to be carried out PSSRU 2011 (ward manager 24hr ward)	Nurse advanced (band 7) (Section 14 of PSSRU 2017) Cost per hour of patient contact	£131 (Cost per working hour is £54)	£133.34	£133.34
5 hours 1:1 senior nurse care	PSSRU 2011 (ward manager 24hr ward)	Nurse advanced (band 7) (Section 14 of PSSRU 2017) Cost per hour of patient contact	£131 (Cost per working hour is £54)	£133.34	£666.69
10 min overnight junior staff review	PSSRU 2011 (foundation house officer 1)	Foundation doctor (FY1) (Section 15 of PSSRU 2017) Cost per working hour	£26	£26.46	£4.41
				TOTAL	£1052

Table Vb. Breakdown of cost of IV-tPA

IV-tPA	£1743
Drug acquisition	£691.20 900 micrograms required per kg [16]; 75kg/patient; 67.5mg per patient £259.20 for 20mg pack + £432 for 50mg pack =>£691.20 per patient Lower 60kg/patient; 54mg per patient £172.80 for 10mg pack + £432 for 50mg pack => £604.80 Upper 85kg/patient; 76.5mg per patient £172.80 for 10mg pack + £259.20 for 20mg pack + £432 for 50mg pack => £864
Administration	£1,052 Lower: £965 Upper: £1,052
Drug acquisition + administration	Average: 691.2 + 1052 = £1,743.2 Lower: 604.8 + 965 = £1,569.8 Upper: 864 + 1052 = £1,916

Assuming an average patient weight of 75kg, based on an indication of 900 micrograms per kg [17], the average drug acquisition cost was estimated to be £691.20. Assuming alternative weights of 60kg and 85kg led to required doses of 54mg and 76.5mg, respectively. We then assumed a lower estimate of drug acquisition costs to be £604.80 (assuming between 50mg and 60mg are required per patient), and £864 (assuming between 70mg and 80mg are required per patient).

The administration costs, that were based on those from Sandercock et al. study (2004) [15] and inflated for 2018, amount for £1,051.6. Discussion with a clinical expert regarding general changes in the care of stroke patients over time suggests that the difference in care between patients receiving IV-tPA and those not receiving IV-tPA may not anymore be as important as the estimates that Sandercock suggested for the year 2004. In particular, less administrative (145 minutes) and consultant (20 minutes) time should be assumed for patients receiving IV-tPA compared to 2004. Based on this, we estimated a lower estimate of the costs of administration of patients receiving IV-tPA of £965.

Table VI. Distribution of ischemic patients across the mRS scale at three months per prior probability and AdvImg accuracy (results of the model)

	Advanced imaging accuracy	Prior probability	Ischemic patients in mRS 0	Ischemic patients in mRS 1-2	Ischemic patients in mRS 3-4-5	Ischemic patients in mRS 6
CT-CTA and no late MT strategy	NA	10%	15%	36%	35%	13%
	NA	20%	14%	34%	36%	15%
	NA	30%	13%	32%	38%	17%
AdvImg followed by late MT strategy (9 scenarios)	**perfect advanced-imaging test**	10%	16%	39%	33%	12%
		20%	15%	38%	33%	14%
		30%	14%	38%	32%	16%
	sensitivity: 80% specificity: 100%	10%	16%	38%	34%	12%
		20%	15%	38%	34%	14%
		30%	14%	37%	34%	15%
	sensitivity: 100% specificity: 70%	10%	15%	38%	33%	13%
		20%	15%	38%	33%	14%
		30%	14%	38%	33%	15%

NA: not applicable

Table VII. Lifetime costs, LYs and QALYs for the nine investigated scenarios (results of the model)

	pre-test probability	COSTS			LYs			QALYs		
		CCEMT	AIELMT	INCREM.	CCEMT	AIELMT	INCREM.	CCEMT	AIELMT	INCREM.
perfect test	10%	$55.985	$57.245	$1.260	7,186	7,339	0,153	3,732	3,886	0,154
	20%	$55.727	$58.020	$2.293	6,907	7,209	0,302	3,510	3,813	0,303
	30%	$55.474	$58.793	$3.319	6,634	7,081	0,447	3,293	3,741	0,448
se=0,8 sp=1	10%	$55.985	$57.036	$1.051	7,186	7,308	0,122	3,732	3,855	0,123
	20%	$55.727	$57.604	$1.876	6,907	7,148	0,241	3,510	3,752	0,242
	30%	$55.474	$58.169	$2.695	6,634	6,990	0,356	3,293	3,649	0,357
se=1 sp=0,7	10%	$55.985	$60.621	$4.637	7,186	7,226	0,040	3,732	3,826	0,094
	20%	$55.727	$61.014	$5.287	6,907	7,110	0,202	3,510	3,760	0,250
	30%	$55.474	$61.407	$5.932	6,634	6,994	0,360	3,293	3,695	0,402

Table VIII. ICERS at 90 days and lifetime horizon for the nine investigated scenarios (results of the model)

	ICER (cost per LY gained) lifetime			ICER (cost per QALY gained) lifetime		
	se=1 sp=1	se=0,8 sp=1	se=1 sp=0,7	se=1 sp=1	se=0,8 sp=1	se=1 sp=0,7
pre-test proba = 30%	3 months $240.245 lifetime $7.424	3 months $245.411 lifetime $7.565	3 months $805.037 lifetime $16.465	3 months $131.805 lifetime $7.410	3 months $134.640 lifetime $7.557	3 months $322.752 lifetime $14.765
pre-test proba = 20%	3 months $250.578 lifetime $7.586	3 months $258.328 lifetime $7.780	3 months $1.811.967 lifetime $26.113	3 months $137.474 lifetime $7.569	3 months $141.726 lifetime $7.767	3 months $494.846 lifetime $21.156
pre-test proba = 10%	3 months $281.579 lifetime $8.221	3 months $297.079 lifetime $8.586	3 months -$4.280.241 lifetime $115.077	3 months $154.482 lifetime $8.199	3 months $162.986 lifetime $8.566	3 months $1.258.398 lifetime $49.515

Methods and sources used to calculate the probabilities of the decision tree

Calculation of the probability that the ischemic patient imaged within 4,5 hours receives IV-tPA:

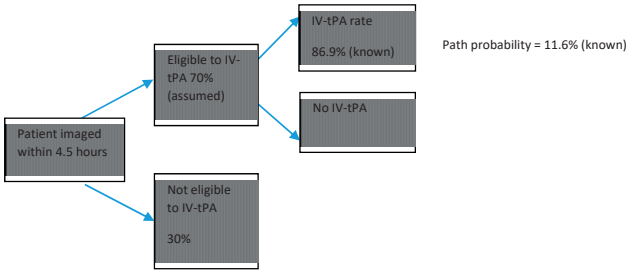
We assumed that 70% of the ischemic stroke patients managed within 4,5 hours were eligible to IV-tPA (in reference to the fact that 80+ patients should be considered on individual basis).

The percentage of all stroke patients (all stroke types) given thrombolysis (April 2016-March 2017) is 11.6%.

The percentage of eligible patients (according to the Royal College of Physicians guideline minimum threshold) given thrombolysis (April 2016-March 2017) is 86.9%.

Based on these proportions, we calculated the probability that the ischemic patient imaged within 4,5 hours receives IV-tPA.

Figure: path probabilities



Based on the above data:
Probability that the ischemic patient imaged within 4,5 hours receives IV-tPA
= (86.9*70/100)/100
= 0.608

This appeared to be consistent with the study by Mc Meekin et al. [18]. They reported that:
- the early presenters (within 4 hours) were 15350.
- those who received IV-tPA if eligible were 10130
This leads to a probability to receive IV-tPA of 10130/15350= 65.9%.

Calculation of the probability that the ischemic patient is being imaged within 4.5 hours after symptom onset and calculation of the probability that the ischemic patient is being imaged between 4.5 and 6 hours after symptom onset

1. The distribution of onset to hospital times is known (figure below)
2. The probability to receive a scan within 1 hour once the patient is in the hospital is known (51.3%)
based on these, we estimated the distribution from onset to CT times
3. Assumptions:
3a. the distribution of patients with known and unknown onset time is the same among ischemic and hemorrhagic patients.
3b. we found in the literature the proportion of patients per hour range from onset to hospital arrival (for patients with known onset). In each hour range, we assumed that the proportion of patients in the first half hour equals the proportion of patients in the second half hour.
3c. finally, we assumed that the probability for a patient to receive a scan within 1 hour is related to the time from symptom onset to arrival at hospital. Patients that have a shorter time since onset are more likely to receive a scan within 1 hour than those who had their onset a longer time ago. Therefore, we assumed that the probability to receive a scan within 1 hour when the time from onset is below 3.5 hours was 60%.

Table IX. Data

Values	Reference
Percentage of patients scanned within 1 hour of arrival at hospital: 2016/2017: 51.3%	The Fourth SSNAP Annual Report https://www.strokeaudit.org/Documents/AnnualReport/2016-17-SSNAP-Annual-Report.aspx
32% of patients had an unknown stroke onset 68% had a precise or best estimate of the stroke onset time	https://www.strokeaudit.org/getattachment/AnnualReport/Historical-Guideline/Apr2014Mar2015-AnnualReport.pdf.aspx
Distribution of onset to arrival at hospital time Time from onset to arrival < 3.5 hours: 59% Time from onset to arrival known and >3.5 hours: 41% Time from onset to arrival between 3.5 and 5 hours: 8.5%	https://www.strokeaudit.org/AnnualReport/Historical.aspx figure 4: Symptom onset time to arrival at hospital, for patients with known or estimated onset time
Calculation:	
probability that the ischemic patient is being imaged within 4.5 hours after symptom onset = probability that the time from onset is known * probability that the time from onset is less than 3.5 hours * probability that the patient receives a scan within 1 hour of hospital admission = 0.68 * 0.59 *0.6 = 0.24 **probability that the ischemic patient is being imaged between 4.5 and 6 hours after symptom onset = 0.68 * 0.085 * 0.6 = 0.034**	

Calculation of the conditional probabilities that the ischemic patient receives MT

The calculation of the probabilities to have a thrombectomy within and beyond 4.5 hours and with or without IV-tPA (among all thrombectomies) was based on some known proportions and complemented by assumptions.

1. The total number of thrombectomies from April 2016 to March 2017 was 580. The number of thrombectomies with IV t-PA is known (369 per year, 63.6% of all thrombectomies). It was assumed that thrombectomies performed after IV t-PA were administered either right after thrombolysis or in a delay of maximum 6 hours.
2. It was assumed that 75% of the thrombectomies performed without IV t-PA happened between 4.5 and 6 hours from symptom onset. The remaining 25% of the thrombectomies performed without IV t-PA happened within 4.5 hours from onset.

Table X: Data

	Total	Probabilities among all thrombectomies	References
Thrombectomies	580	100%	https://www.strokeaudit.org/results/Clinical-audit/National-Results.aspx Thrombectomy Report for April 2016 - March 2017
Thrombectomies after IV t-PA	369	63.6%	
Thrombectomies without IV t-PA	211	36.4%	
Thrombectomies without IV t-PA beyond 4.5 hours (and within 6 hours)	158	27.3%	Assumed
Thrombectomies without IV t-PA within 4.5 hours	53	9.1%	Assumed

Table XI: Data

	Thrombectomies after IV t-PA	Thrombectomies without IV t-PA	Total thrombectomies with and without IV t-PA
Thrombectomies within 4.5 hours	369 (63.6%)	53 (25%*36.4% = 9.1%)	-
Thrombectomies between 4.5 and 6 hours		158 (75%*36.4% = 27.3%)	-
Total thrombectomies within and after 4.5 hours	369 (63.6%)	211 (36.4%)	580 (100%)

Table XII: Data

	Probability among all thrombectomies
Thrombectomies without IV t-PA within 4.5 hours	9.1%
Thrombectomies without IV t-PA between 4.5 and 6 hours	27.3%
Thrombectomies after IV t-PA	63.6%

Table XIII: Data

all strokes (England, Wales, Northern Island)	85122
ischemic stroke patients	74216
hemorrhagic stroke patients	10906

3. The 3 conditional probabilities of interest used in the decision tree were back-calculated using the conditional probabilities in the related branches.
3a. Probability that the ischemic patient imaged within 4.5 hours receives MT any time after IV t-PA:
Probability to be imaged within 4.5 hours * Probability to receive IV t-PA * Probability to have a MT after IV t-PA = percentage of ischemic stroke patients receiving MT after IV t-PA
Hence:
Probability to have a MT after IV t-PA
= percentage of ischemic stroke patients receiving MT after IV t-PA / (Probability to be imaged within 4.5 hours * Probability to receive IV t-PA)
= (369/74216)/(0.24*0.60)
= 0.034

3b. Probability that the ischemic patient imaged within 4.5 hours receives MT alone (without IV t-PA):
Probability to be imaged within 4.5 hours * Probability to receive MT within 4.5 hours = percentage of ischemic stroke patients receiving MT within 4.5 hours without IV-tPA
Hence:
Probability to have a MT within 4.5 hours from onset (without IV t-PA)
= percentage of ischemic stroke patients receiving MT within 4.5 hours without IV-tPA /
Probability to be imaged within 4.5 hours
= (53/74216)/0.24
= 0.0029

3c. Probability that the ischemic patient imaged beyond 4.5 hours receives MT between 4.5 and 6 hours from symptom onset (without IV t-PA):
Probability to be imaged beyond 4.5 hours * Probability to receive care between 4.5 and 6 hours * Probability to receive MT between 4.5 and 6 hours = percentage of ischemic stroke patients receiving MT beyond 4.5 hours without IV t-PA
Hence:
Probability to have a MT between 4.5 and 6 hours from onset (without IV t-PA)
= percentage of ischemic stroke patients receiving MT beyond 4.5 hours without IV t-PA/
(Probability to be imaged beyond 4.5 hours* Probability to receive care between 4.5 and 6 hours)
= (158/74216)/(0.76*0.034)
=0.08

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5

Cost-effectiveness of mechanical thrombectomy more than 6 hours after symptom onset among patients with acute ischemic stroke [based on the DAWN and DEFUSE 3 results]

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Key points

Question: Is mechanical thrombectomy in the extended treatment window cost-effective across patient subgroups in the United States?

Findings: This economic evaluation study found that mechanical thrombectomy provides good value for money in all the defined subgroups the 2 randomized clinical trials evaluated. Sensitivity analyses revealed a wide range of probabilities for late mechanical thrombectomy to be cost-effective at the willingness-to-pay threshold of $50 000 per quality-adjusted life-year.

Meaning: The results of this study suggest that attention should be placed on increasing access to mechanical thrombectomy rather than on developing subgroup-specific guidelines unless workforce and budget constraints require prioritization.

Abstract

Importance

Two 2018 randomized controlled trials (DAWN and DEFUSE 3) demonstrated the clinical benefit of mechanical thrombectomy (MT) more than 6 hours after onset in acute ischemic stroke (AIS). Health-economic evidence is needed to determine whether the short-term health benefits of late MT translate to a cost-effective option during a lifetime in the United States.

Objective

To compare the cost-effectiveness of 2 strategies (MT added to standard medical care [SMC] vs SMC alone) for various subgroups of patients with AIS receiving care more than 6 hours after symptom onset.

Design, Setting, and Participants

This economic evaluation study used the results of the DAWN and DEFUSE 3 trials to populate a cost-effectiveness model from a US health care perspective combining a decision tree and Markov trace. The DAWN and DEFUSE 3 trials enrolled 206 international patients from 2014 to 2017 and 182 US patients from 2016 to 2017, respectively. Patients were followed until 3 months after stroke. The clinical outcome at 3 months was available for 29 subgroups of patients with AIS and anterior circulation large vessel occlusions. Data analysis was conducted from July 2018 to October 2019.

Exposures

MT with SMC in the extended treatment window vs SMC alone.

Main Outcomes and Measures

Expected costs and quality-adjusted life-years (QALYs) during lifetime were estimated. Deterministic results (incremental costs and effectiveness, incremental cost-effectiveness ratios, and net monetary benefit) were presented, and probabilistic analyses were performed for the total populations and 27 patient subgroups.

Results

In the DAWN study, the MT group had a mean (SD) age of 69.4 (14.1) years and 42 of 107 (39.3%) were men, and the control group had a mean (SD) age of 70.7 (13.2) years and 51 of 99 (51.5%) were men. In the DEFUSE 3 study, the MT group had a median (interquartile range) age of 70 (59-79) years, and 46 of 92 (50.0%) were men, and the control group had a median (interquartile range) age of 71 (59-80) years, and 44 of 90 (48.9%) were men. For the total trial population, incremental cost-effectiveness ratios were $662/QALY and $13 877/QALY based on the DAWN and DEFUSE 3 trials, respectively. MT with SMC beyond 6 hours had a probability greater than 99.9% of being cost-effective vs SMC alone at a willingness-to-pay threshold of $100 000/QALY. Subgroup analyses showed a wide range of probabilities for MT with SMC to be cost-effective at a willingness-to-pay threshold of $50 000/QALY, with the greatest uncertainty observed for patients with a National Institute of Health Stroke Scale score of at least 16 and for those aged 80 years or older.

Conclusions and relevance

The results of this study suggest that late MT added to SMC is cost-effective in all subgroups evaluated in the DAWN and DEFUSE 3 trials, with most results being robust in probabilistic sensitivity analyses. Future MT evidence-gathering could focus on older patients and those with National Institute of Health Stroke Scale scores of 16 and greater.

5.1 INTRODUCTION

The randomized clinical trials DAWN and DEFUSE 3 demonstrated superior functional outcomes of mechanical thrombectomy (MT) at 90 days among patients with acute ischemic stroke (AIS) treated 6 to 24 hours after they were last known well (eAppendix in the Supplement) [1-2]. Health-economic evidence is needed to determine whether the short-term functional benefit of late MT translates to cost-effectiveness in the United States over a lifetime. A prolonged MT window implies advanced neuroimaging selection of patients and greater neurology and endovascular staff, which are costly and potentially critical resources. Furthermore, factors such as time from symptom onset, patient characteristics, National Institutes of Health Stroke Scale (NIHSS) score, mode of presentation, imaging criteria, and localization of the occlusion might influence the long-term value of late MT. Analyzing the magnitude of the long-term cost-effectiveness of late window MT per patient subgroup could expand the evidence and help inform allocation of critical resources. The aim of this study was to compare the cost-effectiveness of MT with standard medical care (SMC) vs SMC alone by patient subgroup in the late window in the United States.

5.2 METHOD

Study design

We framed, structured, populated and dealt with uncertainty, according to the formal steps of cost-effectiveness modeling [3,4]. A short-run decision tree model (3-month time horizon) and a lifetime Markov state-transition model were designed in Microsoft Excel version 2002 to analyze and compare the costs and outcomes of 2 care pathways, ie, MT with SMC vs SMC alone, in patients with AIS 6 to 24 hours after symptom onset in the United States. We defined SMC as antiplatelet therapy and supportive care according to local guidelines. Subgroup analyses were performed based on the subgroup data published for the 2 trials [1,2]. A hypothetical US cohort of 1000 patients with AIS was modeled using the same age characteristics and criteria as defined in the trials. The efficacy data from the 2 trials were used as 3-month input parameters in our short-run model. Other input parameter values, such as costs, utilities, and transition probabilities, were drawn from the literature. Costs and quality-adjusted life-years (QALYs) were calculated for each care strategy for a lifetime time horizon. Costs and outcomes were discounted at 3% annually, and the US health care perspective was used. Per our institutional policy, ethical approval is not required for this study type. This study followed the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) reporting guideline [5].

Model structure

Decision tree model

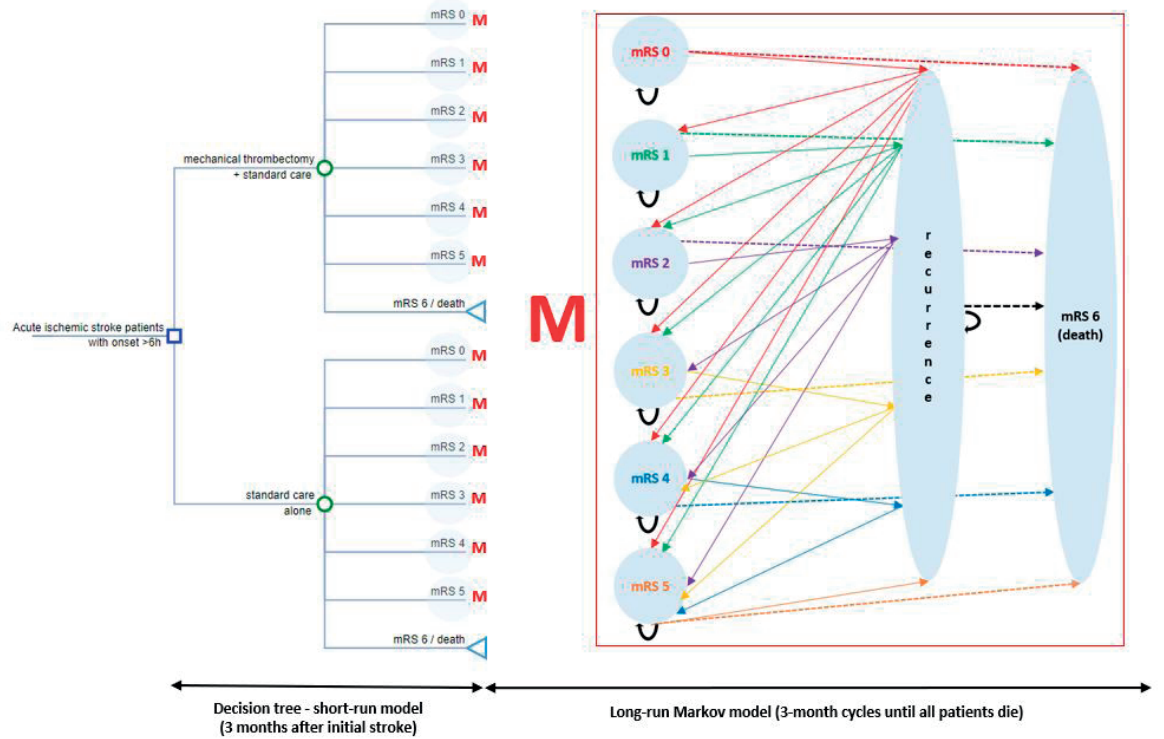
We built a short-run decision model to estimate the costs and clinical outcomes at 90 days after the first AIS (Figure 5.1). Patients with AIS in a hypothetical cohort were distributed at 90 days into 1 of 7 possible modified Ranking Scale (mRS) scores [6]. Treatment outcomes were assumed to occur during the acute phase. The probabilities for a patient to be allocated to the different mRS states at 90 days were obtained from the DAWN and DEFUSE 3 results for both the total study populations and for patient subgroups (eTable 1 in the Supplement). The group of patients in the combined mRS 5 and 6 group in the DAWN results was split into 2 groups (mRS 5 and mRS 6) according to the relative proportions of these 2 groups in the DEFUSE 3 trial. The mean age of the modeled cohort of AIS patients was customized based on the mean age per trial, per strategy (MT with SMC or SMC alone) and per patient subgroup. The ages modeled in our different analyses can be found in eTable 2 in the Supplement.

Markov model

We included AIS patients who survived the initial 3-month acute phase in a long-run Markov state-transition model (Figure 5.1) built to estimate lifetime costs and health outcomes. The model was composed of 3-month cycles, which were repeated until all patients theoretically died to reflect a lifetime time horizon. Every 3 months, patients could remain in their current mRS state, experience a recurrent stroke, or die from nonstroke-related cause. Patients experiencing a recurrent stroke could either die or transition to a worse mRS state (with an equal risk of transitioning to a worse state). Because previous studies indicated an increased mortality for dependent patients (ie, patients with mRS 3, 4, or 5) compared with independent patients (ie, patients with mRS 0, 1, or 2) [7, 8], we used mRS state-specific hazard ratios (Table 5.1) [8-19]. We used US life tables for age-adjusted and sex-adjusted all-cause mortality rates applied from the end of month 3 onward [20].

Patients experiencing a recurrent stroke were managed with the same treatment strategy (ie, MT with SMC or SMC only) as their initial treatment strategy. Based on previous studies, the risk of stroke recurrence was assumed to be equal across mRS states [11, 21]. We assumed that patients could experience only 1 recurrent stroke per 3-month cycle. The transition probabilities used in the Markov model can be found in Table 5.1.

Figure 5.1 Model structure representing the 3-month acute phase and the long-term sequence of events post-initial stroke



Patient's entry into the model occurs at presentation with acute ischemic stroke between 6 and 24 hours after stroke onset. Patients receive either mechanical thrombectomy with standard care or standard care alone as acute treatment and enter a health state of the modified Rankin Scale (mRS) after the 3-month acute phase. Patients who survive the initial acute phase enter the Markov model, which runs on 3-month cycles. After every 3 months, patients can remain in their current mRS state, experience a recurrent stroke, or die from a nonstroke-related cause. After a recurrent stroke, patients either die or transition to a worse mRS state (with risk equally divided among worse states).

□ Decision node, ○ chance node, ◁ terminal node, and M Markov node.

Costs and resource inputs

All costs were calculated in US dollars for the fiscal year 2019. We inflated costs originating from previous years based on the general Consumer Price Index [22]. Costs and resource used in the model are presented in Table 5.1.

For SMC alone, patients were assumed to have received computed tomography (CT) and CT angiography (CTA). For MT with SMC, patients were assumed to have received CT and CTA or magnetic resonance angiography (MRA) and CT perfusion (CTP) or MR imaging (MRI). We assumed that CTA was used as often as MRA and that CTP was used as often as MRI. The cost of the software used to assess the infarct volume with MRI and CTP was added (eTable 3 in the Supplement). The cost of intravenous thrombolysis included acquisition and administration [14]. This cost was included in both the MT with SMC and SMC strategies proportionally to the frequency of use in each group of the DAWN and DEFUSE 3 trials (eTable 4 in the Supplement). The cost of MT included the cost of the devices, nonphysician room personnel, and operating room overhead [15]. The physician costs related to the delivery of MT were added [15].

Based on the literature, the mean acute costs of the first 90 days after AIS and the mean 3-month long-term costs were dependent on the severity of the outcome (ie, on mRS state). The acute costs reflected the mean payment per patient with ischemic stroke older than 65 years discharged to home after hospitalization with an mRS score of less than 2, discharged to any destination except home with an mRS score of 3 to 5, and dying at the hospital with an mRS score of 6, based on original data from the 2010 to 2013 MarketScan Commercial Claims and Encounters Inpatient Database and Medicare Supplemental and Coordination of Benefits Database [16, 23]. Long-term mRS state-specific poststroke costs were based on observed data from a prospective economic study conducted alongside the SWIFT-PRIME trial [24]. The long-term costs were based on Medicare inpatient and outpatient claims 3 months after the initial hospitalization and until death for 958 patients treated in 2 stroke centers in the United-States between 2010 and 2014 [15]. Nursing home costs were included. The cost of a recurrent stroke was derived from the findings of the decision tree and assumed to be specific to the MT with SMC strategy or SMC strategy alone. As such, it represents the cost estimate to identify and treat a typical AIS according to the strategy defined in the decision tree.

Table 5.1 List of input parameters[a]

Model input parameters	Base-Case value	Distribution	Range	Source
3-monthly transition probabilities in the Markov model				
State after recurrence of a patient in mRS 0		Dirichlet	0-1	[9,10] Fagan et al. for probability of death and assumption that the patient has an equal risk of transitioning to one of the worse states
mRS 1	0.19			
mRS 2	0.19			
mRS 3	0.19			
mRS 4	0.19			
mRS 5	0.19			
mRS 6 or death	0.0513			
State after recurrence of a patient in mRS 1		Dirichlet	0-1	
mRS 2	0.24			
mRS 3	0.24			
mRS 4	0.24			
mRS 5	0.24			
mRS 6 or death	0.0513			
State after recurrence of a patient in mRS 2		Dirichlet	0-1	
mRS 3	0.32			
mRS 4	0.32			
mRS 5	0.32			
mRS 6 or death	0.0513			
State after recurrence of a patient in mRS 3		Dirichlet	0-1	
mRS 4	0.47			
mRS 5	0.47			
mRS 6 or death	0.0513			
State after recurrence of a patient in mRS 4		β	α: 94.9 β: 5.1	
mRS 5	0.95			
mRS 6 or death	0.0513			
Death hazard ratios for mRS 0 / mRS 1 / mRS 2 / mRS 3 / mRS 4 / mRS 5	1 / 1 / 1.11 / 1.27 / 1.71 / 2.37	Log normal	SE: 0.076 / 0.46 / 0.46 / 0.46 / 0.46 / 0.46	[8] Samsa et al., 1999
Recurrence	0.013	β	α: 13 β: 986	[11] Ganesalingam et al., 2015

Table 5.1 List of input parameters[a] (*continued*)

Model input parameters	Base-Case value	Distribution	Range	Source
Costs and resource use				
Costs and resource use in the decision tree				
CT	$198	β Pert	$168-$228	[12] CMS 2015
CTA	$774	β Pert	$658-$890	
MRI	$625	β Pert	$531-$718	
MRA	$1023	β Pert	$870-$1.176	
CTP	$836	β Pert	$711-$961	[13] Jackson et al., 2010
Software	$89	β Pert	($44 – 520)	eTable 3 in the Supplement
Frequency of CTA vs MRA	0.5	Uniform	0-1	Assumed
Frequency of CTP vs MRI	0.5	Uniform	0-1	Assumed
IV-tPA acquisition and administration	$8004	β Pert	$6403-$9605	[14] Kunz et al., 2016
MT devices, nonphysician room personnel, and operating room overhead	$15836	β Pert	$5270-$26401	[15] Shireman et al., 2017
physician costs	$2749	β Pert	$1262-$4236	
Acute first 3-month costs				[16] Joo et al., 2017 (No IV-tPA group, weighted mean of costs for the group aged 65-80 years and the group aged above 80 years)
mRS 0	$14382	β Pert	$14210-$14554	
mRS 1	$14382	β Pert	$14210-$14554	
mRS 2	$14382	β Pert	$14210-$14554	
mRS 3	$17879	β Pert	$17660-$18097	
mRS 4	$17879	β Pert	$17660-$18097	
mRS 5	$17879	β Pert	$17660-$18097	
mRS 6 or death	$23498	β Pert	$22614-$24382	
Costs and resource use in the Markov model				
3-monthly long-term healthcare costs, day 90 onward				
mRS 0	$2836	β Pert	$2269-$3403	[15] Shireman et al., 2017
mRS 1	$2741	β Pert	$2336-$3504	
mRS 2	$3378	β Pert	$2703-$4054	[17] Earnshaw et al., 2009 for range
mRS 3	$5801	β Pert	$4641-$6961	
mRS 4	$11742	β Pert	$9393-$14090	
mRS 5	$17262	β Pert	$13809-$20714	

Table 5.1 List of input parameters[a] (*continued*)

Model input parameters	Base-Case value	Distribution	Range	Source
Cost of recurrent stroke (90 days following stroke recurrence)	Values for the total population:	No independent distribution was defined. Costs vary based on the 2000 PSA results (ie, expected value of costs) of decision tree.	Based on the 95% CIs of the 2000 PSA results:	From short-run 90-day decision-tree
In the MT+SMC strategy	$37974 (DAWN) $38500 (DEFUSE 3)		$29607-$47008 $30077-$47738	
In the SMC alone strategy	$20693 (DAWN) $20479 (DEFUSE 3)		$20073-$21378 $19834-$21198	
Utilities				
mRS 0	0.85	β	0.8 - 1	[18] Gage et al., 1998
mRS 1	0.8	β	0.8 - 0.95	
mRS 2	0.7	β	0.68 - 0.9	[19] Nelson et al., 2016
mRS 3	0.51	β	0.45 - 0.65	
mRS 4	0.3	β	0.1 - 0.4	[17] Earnshaw et al., 2009 for the range.
mRS 5	0.15	β	0 - 0.32	
mRS 6 or dead	0	NA	NA	
Recurrent stroke (90 days following stroke recurrence)				
	Values for the total population:	No independent distribution was defined. Utilities vary based on the 2000 PSA results (ie expected value of utility) of the decision tree.	Based on the 95% CIs of the 2000 PSA results:	From short-run 90-day decision-tree
In the MT+SMC strategy	0.49 (DAWN) 0.48 (DEFUSE 3)		0.43-0.56 0.42-0.56	
In the SMC alone strategy	0.31 (DAWN) 0.31 (DEFUSE 3)		0.24-0.37 0.24-0.37	

[a] Input parameters related to efficacy of MT with SMC and SMC alone, used in the decision tree, can be found in eTable 1 in the supplemental.

Abbreviations:

CT, computed tomography; CTA, CT angiography; CTP, CT perfusion; IV-tP, intravenous tissue plasminogen activator; MRA, magnetic resonance angiography; MRI, MR imaging; mRS, modified Ranking Scale; MT, mechanical thrombectomy; SMC, standard medical care.

Utilities and quality of life

Utilities were assigned to each mRS state based on survey data from a large sample of individuals at increased risk of stroke using the time trade-off method to value hypothetical health states. We chose this because of its methods and its use in recent US cost-effectiveness models [18, 19].

Utility values (ranges) were defined as 0.85 (0.80-1.00) for mRS 0; 0.80 (0.80-0.95) for mRS 1; 0.70 (0.68-0.90) for mRS 2; 0.51 (0.45-0.65) for mRS 3; 0.30 (0.10 to 0.40) for mRS 4; and 0.15 (0-0.32) for mRS 5. The utility of a recurrent stroke was assumed to be specific to each pathway and derived from the outcomes of the short-run model. Utilities were varied according to a β distribution (Table 5.1).

Subgroup analyses

The published results of the DAWN and DEFUSE 3 trials allowed for 29 subgroup analyses. The mean ages reported for the total study population from the trials (control and intervention groups) were used by default except for subgroups defined by age (eTable 2 in the Supplement). The sample size for each subgroup was modeled according to the trial subgroups (eTable 1 in the Supplement). Cost-effectiveness analyses were conducted for the total study populations and patient subgroups defined by time from stroke onset, age, NIHSS score, mode of presentation, clinical infarct mismatch (group A, aged ≥80 years, NIHSS score ≥10, and infarct volume <21 mL; group B, aged <80 years, NIHSS score ≥10, and infarct volume <31 mL; group C, aged <80 years, NIHSS score ≥20, and infarct volume 31-51 mL), occlusion location, time of symptom first observed, and trial eligibility criteria.

Statistical analysis

No statistical tests were conducted. No hypothesis testing nor level of statistical significance was relevant to our analysis. We estimated the credibility intervals (CI) surrounding the mean values when relevant (Table 5.2).

We performed a probabilistic sensitivity analysis (PSA) in Excel to assess how parameter uncertainty affected the cost-effectiveness results. In this process, we assigned a distribution to each parameter according to the level of uncertainty regarding its deterministic value. A random value was drawn from each distribution, and the set of drawn values was used to calculate the results of interest. This process was repeated in 2000 simulations to generate 2000 estimates of the costs and QALYs for each strategy. The proportion of simulations when MT with SMC had a higher net monetary benefit (NMB) than SMC alone was calculated for different values of the willingness-to-pay (WTP) threshold for a QALY. The results were described using cost-effectiveness acceptability curves, in which

Table 5.2 Expected values of cost-effectiveness of mechanical thrombectomy with standard medical care vs standard medical care alone per patient with acute ischemic stroke stratified per subgroup in the base case

		DAWN				DEFUSE 3			
subgroups according to criteria		Incremental costs (95% CI), $	Incremental QALY (95% CI)	ICER ($/QALY)	Incremental NMB 95% CI), $[a]	Incremental costs (95% CI), $	Incremental QALY (95% CI)	ICER ($/QALY)	Incremental NMB 95% CI), $[a]
Time from stroke onset, h[b]	6 ≤ 24 hours (full DAWN group)	1380 (-62 510 to 52 675)	2.085 (1.283 to 3.239)	662	207 125 (121 419 to 328 519)	NA	NA	NA	NA
	6 ≤ 12 hours	-24 340 (-109 596 to 51 786)	1.968 (0.793 to 3.403)	-12 369 (dominant)	221 130 (87 319 to 389 968)	NA	NA	NA	NA
	>12 hours	23 446 (-46 225 to 85 923)	2.244 (1.259 – 3.468)	10 063	200 996 (88 012 to 340 344)	NA	NA	NA	NA
	6 ≤ 16 hours (full DEFUSE 3 group)	NA	NA	NA	NA	25 098 (-35 502 to 76 710)	1.809 (0.972 to 2.847)	13 877	155 767 (63 411 to 277 583)
	6 ≤ 11 hours	NA	NA	NA	NA	8 511 (-62 240 to 71 472)	1.086 (-0.036 to 2.387)	7838	100 076 (-26 195 to 247 802)
	>11 hours	NA	NA	NA	NA	49 256 (-32 490 to 128 731)	2.599 (1.453 to 4.016)	18 951	210 654 (85 444 to 366 389)
Age (years)	≥ 80	14 451 (-38 704 to 58 813)	0.677 (-0.11 to 1.666)	19 994	57 825 (-23 371 to 153 740)	10 957 (-45 627 to 59 194)	0.504 (-0.256 to 1.376)	21 733	39 461 (-48 722 to 198 257)
	<80 years	-28 675 (-106 405 to 36 384)	2.062 (1.043 to 3.344)	-13 908 (dominant)	234 857 (114 005 to 388 901)	29 235 (-40 244 to 89 664)	1.930 (0.906 to 3.214)	15 151	163 727 (45 800 to 314 595)
NIHSS score	10 to <17	-14 030 (-91 236 to 47 696)	2.4972 (1.331 to 3.932)	-5 675 (dominant)	261 266 (129 596 to 424 608)	NA	NA	NA	NA
	≥17	18 125 (-62 348 to 81 368)	1.427 (0.472 to 2.581)	12 698	124 620 (24 100 to 258 074)	NA	NA	NA	NA
	<16	NA	NA	NA	NA	5 473 (-62 186 to 61 355)	1.540 (0.363 to 2.871)	3555	148 488 (10 890 to 304 083)
	≥16	NA	NA	NA	NA	56 866 (-21 042 to 132 049)	1.334 (0.256 to 2.443)	42 635	76 514 (-42 001 to 196 691)
Mode of presentation	Wake up	-9275 (-88 519 to 58 881)	2.241 (1.172 to 3.549)	-4139 (dominant)	233 341 (119 290 to 386 019)	10 318 (-81 241 to 82 859)	1.949 (0,891 to 3,355)	5294	184 593 (73 893 to 338 877)
	Witnessed	13 005 (-117 373 130 783)	2,921 (0.786 to 5.218)	4453	279 067 (36 291 537 288)	21 061 (-57 981 to 93 981)	2.143 (0.721 to 3.738)	9828	193 230 (24 396 to 377 276)
	Unwitnessed	9522 (-86 403 to 95 731)	1.507 (0.094 to 3.044)	6319	141 170 (-12 913 312 454)	NA	NA	NA	NA
Clinical infarct mismatch[c]	Group A	14 451 (-35 197 56 392)	0.723 (-0,022 1,623)	19 994	57 825 (-20 168 153 024)	NA	NA	NA	NA
	Group B	-28 621 (-106 109 37 741)	1.988 (0.95 to 3.348)	-14 397 (dominant)	227 428 (106 248 387 532)	NA	NA	NA	NA
	Group C	-22 379 (-214 699 145 798)	1.380 (-1.639 to 4.234)	-16 211 (dominant)	160 340 (-153 172 480 987)	NA	NA	NA	NA
Occlusion location	ICA	22 813 (-80 872 118 427)	1.930 (0.149 to 4.018)	11 819	170 202 (-19 862 383 228)	NA	NA	NA	NA
	MCA M1	804 (-66 161 56 198)	1.982 (1.097 to 3.162)	406	197 363 (91 793 330 057)	NA	NA	NA	NA
	MCA M2	-49 769 (-283 278 189 815)	1.782 (-3.319 to 6.476)	-27 934 (dominant)	227 933 (-303 565 711 711)				
Time of symptom first observed, h[d]	≤6 hours	9 340 (-61 634 67 879)	2.006 (1.083 to 3.245)	4657	191 216 (81 783 334 672)	NA	NA	NA	NA
	>6 hours	-18 671 (-115 297 60 878)	2.367 (1,01 to 3,96)	-7888 (dominant)	255 379 (104 956 429 484)	NA	NA	NA	NA
Trial eligibility criteria	Not DAWN eligible	NA	NA	NA	NA	46 853 (-34 763 to 119 181)	1.972 (0.577 to 3.602)	23 763	150 317 (-4487 to 326 266)
	DAWN eligible	NA	NA	NA	NA	11 420 (-59 575 to 68 490)	1.589 (0.622 to 2.778)	7186	147 497 (36 712 to 282 645)

Abbreviations: ICA, internal carotid artery; ICER, incremental cost-effectiveness ratio; MCA, middle cerebral artery; NA, not applicable; NIHSS, National Institutes of Health Stroke Scale; NMB, net monetary benefit; QALY, quality-adjusted life-year.

[a] NMB set at a willingness-to-pay threshold of $100 000/QALY.

[b] Time from stroke onset to randomization. Data from the DAWN trial were used to estimate the cost-effectiveness of mechanical thrombectomy with standard medical care vs standard medical care alone. These results are presented for patients treated between 6 and 24 hours, between 6 and 12 hours, and between 12 and 24 hours from stroke onset. Data from the DEFUSE 3 trial were used to estimate the cost-effectiveness of mechanical thrombectomy with standard medical care vs standard medical care alone for patients treated between 6 and 16 hours, between 6 and 11 hours, and between 11 and 16 hours from stroke onset. The same logic applies to the other subgroups per trial defined according to the different criteria presented in the first column.

[c] Clinical infarct mismatch indicates a mismatch between the severity of the clinical deficit and the infarct volume defined according to the following groups: A, aged 80 years and older, NIHSS score of at least 10, and infarct volume of less than 21 mL; B, younger than 80 years, NIHSS score of at least 10, and infarct volume of less than 31 mL; C, younger than 80 years, NIHSS score of at least 20, and infarct volume between 31 and 51 mL.

[d] Time of symptom first observed to randomization.

each curve represented the probability that MT with SMC was cost-effective compared with SMC alone at different WTP thresholds.

5.3 RESULTS

In the DAWN study, the MT group had a mean (SD) age of 69.4 (14.1) years and 42 of 107 (39.3%) were men, and the control group had a mean (SD) age of 70.7 (13.2) years and 51 of 99 (51.5%) were men. In the DEFUSE 3 study, the MT group had a median (interquartile range) age of 70 (59-79) years, and 46 of 92 (50.0%) were men, and the control group had a median (interquartile range) age of 71 (59-80) years, and 44 of 90 (48.9%) were men.

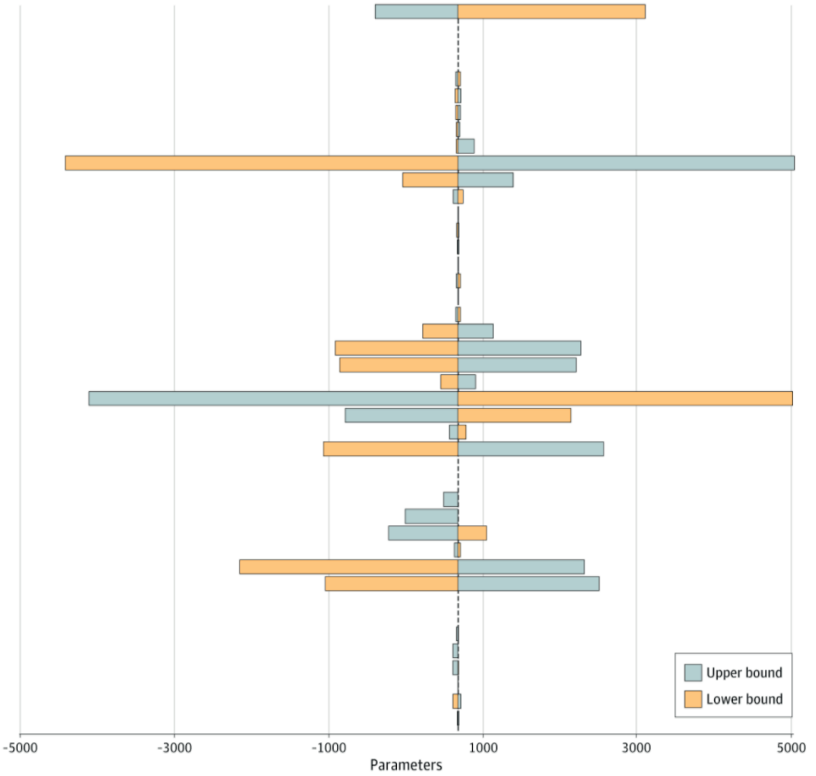
Table 5.2 shows the base-case cost-effectiveness results of MT with SMC vs SMC alone per trial inputs. Based on the total population from either trial, MT with SMC generated higher costs and more QALYs compared with SMC alone. The resulting incremental cost-effectiveness ratios (ICERs) were $662/QALY and $13 877/QALY based on the DAWN and DEFUSE 3 trial inputs, respectively. The incremental costs and QALYs for the total populations and all subgroups are plotted in eFigure 1 in the Supplement. In all subgroups, MT with SMC led to better health outcomes than SMC alone. In 8 of 18 DAWN subgroups (44.4%), MT with SMC was cost saving and more effective (ie, dominant) compared with SMC alone. Based on the DEFUSE 3 trial results, $3555 was the minimum cost to gain 1 QALY and was observed in patients with baseline NIHSS scores of less than 16. The maximum cost to gain 1 QALY was $19 994, based on the DAWN results and observed for patients older than 80 years and those in clinical infarct mismatch group A. Based on the DEFUSE 3 results, the maximum cost to gain 1 QALY was $42 635 for patients with baseline NIHSS score of 16 or greater (Table 5.2).

Figure 5.2 presents the results of the deterministic 1-way sensitivity analysis based on the DAWN inputs. The ICER is particularly sensitive to the cost of MT. Additionally, an increase in the long-term cost of mRS 4 and 5 led to a more favorable ICER. The same analysis based on the DEFUSE 3 inputs led to similar results (eFigure 2 in the Supplement).

The uncertainty surrounding the base-case estimates for the total population per trial is shown in Figure 5.3A. The PSA demonstrated that MT with SMC had either a 100% (based on the DAWN results) or a 99.9% (based on the DEFUSE 3 results) probability of being cost-effective at the WTP threshold of $100 000 per QALY. At a threshold of $50 000 per QALY, the probability of MT with SMC to be cost-effective was 100% and 97.5% based on the DAWN and DEFUSE 3 results, respectively. Scatter plots of incremental costs and incremental QALYs for all subgroups per trial can be found in eTable 5 in the Supplement.

Figure 5.2 One-way sensitivity analysis based on the DAWN inputs

Efficacy	Bounds
MT+SMC	Low efficacy to high efficacy
Costs	
CT	$168-$228
CTA	$658-$890
MRA	$870-$1176
CT perfusion	$711-$961
MRI	$531-$718
RAPID software	$44-$520
MT	$5270-$26 401
Physician	$1262-$4236
Cost IV-tPA	$6403-$9605
Acute costs, mRS 0	$14 210-$14 554
Acute costs, mRS 1	$14 210-$14 554
Acute costs, mRS 2	$14 210-$14 554
Acute costs, mRS 3	$17 660-$18 097
Acute costs, mRS 4	$17 660-$18 097
Acute costs, mRS 5	$17 660-$18 097
Acute costs, mRS 6	$22 614-$24 382
Long-term costs, mRS 0	$2269-$3403
Long-term costs, mRS 1	$2336-$3504
Long-term costs, mRS 2	$2703-$4054
Long-term costs, mRS 3	$4641-$6961
Long-term costs, mRS 4	$9393-$14 090
Long-term costs, mRS 5	$13 809-$20 714
Cost of recurrence in SMC	$20 073-$21 378
Cost of recurrence in MT+SMC	$29 607-$47 008
Hazard ratios	
mRS 0	1.0-1.2
mRS 1	1.0-1.2
mRS 2	1.0-1.2
mRS 3	1.2-1.4
mRS 4	1.3-2.0
mRS 5	1.5-4.0
Utilities	
mRS 0	0.80-1.00
mRS 1	0.80-0.95
mRS 2	0.68-0.90
mRS 3	0.45-0.65
mRS 4	0.10-0.40
mRS 5	0-0.32



Deterministic 1-way sensitivity analysis of model input parameters grouped by categories based on the DAWN inputs. The plot shows how varying input parameters to the limits reported, 1 at a time, affects the incremental cost-effectiveness ratio (ICER), while keeping all the other model input parameters at their base-case value.

The orange bars represent how the lower bounds affect the ICER, and the blue bars represent how the upper bounds affect the ICER.

The length of the bars reveals the degree of influence that 1 input parameter has on the ICER compared with the base-case ICER of $662 per quality-adjusted life-years.

Low and high efficacy of mechanical thrombectomy with standard medical care (MT+SMC) was defined by the following distribution of patients on the modified Rankin Scale (mRS) at 3 months:

low efficacy, mRS 0, 7%; mRS 1, 20%; mRS 2, 15%; mrS 3, 14%; mRS 4, 14.5%; mRS 5, 11.5%; and mRS 6, 18%; high efficacy, mRS 0, 10%; mRS 1, 23%; mRS 2, 18%; mRS 3, 13%; mRS 4, 12%; mRS 5, 9%; and mRS 6, 15%.

CT indicates computed tomography; CTA, CT angiography; IV-tPA, intravenous tissue plasminogen activator; MRA, magnetic resonance angiography; and MRI, MR imaging.

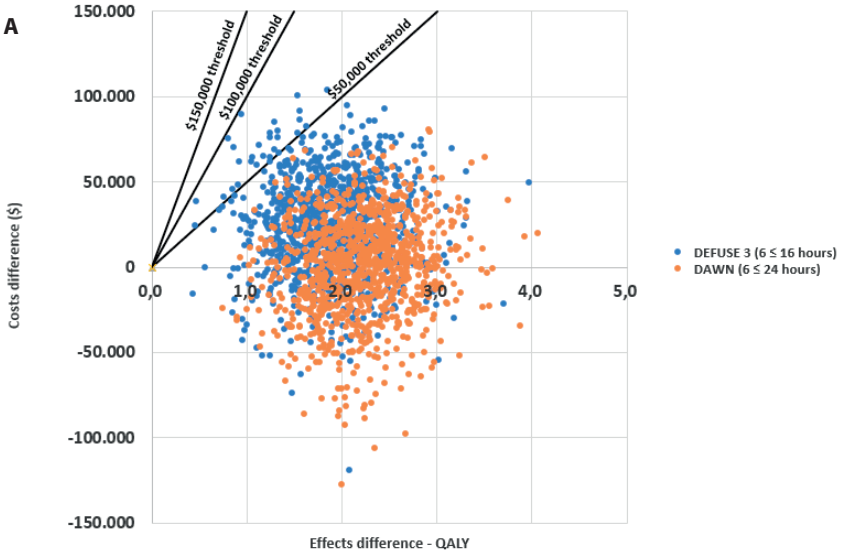
Figure 5.3B shows the probability that MT with SMC is cost-effective at different WTP thresholds for a QALY for the total populations and the 3 subgroups characterized by the most extreme results. At the threshold of $100 000/QALY, the probability for MT with SMC to be cost-effective was among the 2 lowest for patients aged 80 years or older (DEFUSE 3) (83.3%). At this threshold, the lowest probability (79.8%) was observed for patients with a middle cerebral artery M2 occlusion (DAWN), but given the small sample size for this group, its curve is reported only in eFigure 3 in the Supplement. At $50 000/QALY, the probability for MT with SMC to be cost-effective was less than 60% for patients with a baseline NIHSS score of 16 or greater in the DEFUSE 3 trial. At a low or no WTP for a QALY, the probability of MT with SMC being cost-effective was the highest among patients younger than 80 years (DAWN). eFigure 3 in the Supplement presents the consolidated results for all groups and subgroups.

5.4 DISCUSSION

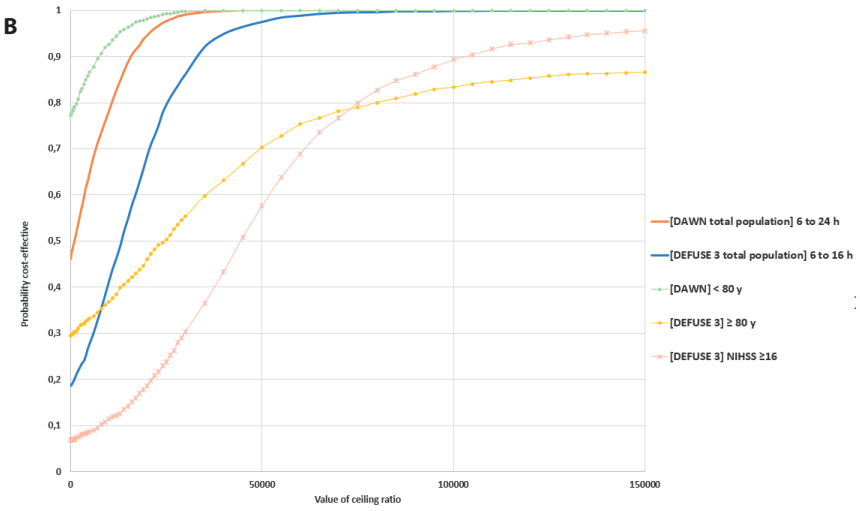
Our main finding was that MT with SMC, compared with SMC alone, for patients with AIS and anterior large vessel occlusion in the late window is cost-effective in the United States. We performed model-based cost-effectiveness analyses of MT with SMC compared with SMC alone based on the DAWN and DEFUSE 3 trial results and found that MT with SMC met conventional standards for cost-effectiveness in all subgroups. Based on the American College of Cardiology and American Heart Association (ACC/AHA) policy statement defining cost-effectiveness levels to inform value-based policies, ICERs below $50 000/QALY suggest high-value care, while ICERs between $50 000/QALY and $150 000 suggest intermediate value [25]. All the point estimates in the various subgroups suggest that MT with SMC provides high-value care (per the ACC/AHA standard) compared with SMC alone. The PSA results indicated that the minimum probability for MT with SMC to be cost-effective was approximately 80% at a threshold of $100 000/QALY across subgroups. Increased uncertainty regarding whether MT with SMC was cost-effective at $50 000/QALY appeared among patients with NIHSS scores of 16 or greater in the DEFUSE 3 trial and patients aged 80 years and older in both trials.

Our findings are consistent with previous studies but also push the boundary of knowledge regarding the cost-effectiveness of late MT. Kunz et al [14] performed a model-based cost-effectiveness analysis of MT with SMC vs SMC in the early treatment window. Their calculated ICER ($3110/QALY) was similar to our findings in the late treatment window ($662/QALY and $13 877/QALY for the DAWN and DEFUSE 3 trials, respectively). Although their analysis was limited by the number of subgroups, their results were robust in most patient profiles. In another analysis in the early window, Kunz et al [26]

Figure 5.3 Monte Carlo simulations of incremental cost and incremental quality-adjusted life-years (QALY) of mechanical thrombectomy with standard medical care for the full population
A. Monte Carlo simulations of incremental cost and incremental QALY
B. Cost-effectiveness acceptability curves



A, The results are shown as scatterplots of incremental costs and incremental QALYs of mechanical thrombectomy with standard medical care vs standard medical care alone per patient with acute ischemic stroke for the full population per trial. Each dot represents 1 simulation run. The black lines indicate 3 different willingness-to-pay thresholds per QALY. The number of dots below a specific line represent the probability for mechanical thrombectomy with standard medical care to be cost-effective at the related WTP threshold.



B, Each curve shows the probability that mechanical thrombectomy with standard medical care is cost-effective at different values of willingness to pay for a QALY for the full population and different subgroups. Curves for the SMC alone strategy are not shown.

found that MT with SMC was cost-effective in all age groups analyzed (ie, 50-100 years at stroke onset), with increased cost-effectiveness observed in younger patients, which is also consistent with our findings. In contrast, Pizzo et al [27] and Peultier et al [28] demonstrated that MT with SMC vs SMC alone was cost-effective in the late window in the United Kingdom. However, by targeting the UK market, their studies may not be generalizable to the US cost structure and did not include subgroups.

Given that they demonstrated the cost-effectiveness of MT across all clinical subgroups, our findings have latent policy and clinical implications. Acute stroke treatment guidelines and quality measures should focus on increasing access to MT for all eligible US patients rather than on tailoring policies that prioritize specific subgroups. Specifically, policies are needed to improve stroke recognition and transportation to comprehensive stroke centers (providing MT) in light of the cost-effectiveness of MT, which does not depreciate significantly by stroke severity or age. Should additional MT trials be conducted, our results suggest potential value in reducing the uncertainty regarding the cost-effectiveness of MT in certain subgroups (ie, patients with NIHSS scores of 16 or greater and those aged 80 years and older). However, this is only important to improve the certainty that MT represents high-value care (ie, ICER <$50 000/QALY), as opposed to MT being cost-effective at the conventional thresholds of $100 000/QALY to $150 000/QALY used in the United States [29].

Beyond the cost-effectiveness considerations, the evidence regarding the clinical effectiveness of MT in the extended time window presents challenges for fast and widespread implementation. Complex and transversal care by ambulance or air and personnel in emergency, neurology, radiology, and neuro-intervention might sometimes be limited and might not guarantee access to MT for all eligible patients. Local and national policies to increase staffing in these professions may be necessary to meet this burgeoning clinical demand. Another short-term way to address potential critical limitations might be to prioritize the delivery of MT according to the degree and certainty of cost-effectiveness per patient subgroup.

Finally, in a country characterized by regions with low population density and large medically underserved areas and many individuals at increased risk of cardiovascular diseases, the delivery of MT in the late window might face organizational challenges [30]. Access to MT for remote patients will probably require more investments in systems such as telemedicine and infrastructures both within and between states. Given that air transportation of patients will decrease time to treatment but increase costs, the optimal organization of stroke care will need to be investigated.

5.5 LIMITATIONS

This study has limitations. First, our analyses are limited by the sample sizes of each subgroup included in the trials. However, we included sample size when estimating the probability of cost-effectiveness and found that there was a high probability that MT with SMC was cost-effective for most subgroups. Second, our analyses were limited by the selections of subgroups reported in the DAWN and DEFUSE 3 trial results. Thus, it is possible that MT with SMC might not be cost-effective in other subgroups. Third, while the DAWN trial included patients from multiple countries, we performed our analyses for the US setting. However, the DEFUSE 3 trial was restricted to 38 stroke centers in the United States, and our findings did not substantially differ between the 2 trials. Fourth, the quality-of-life estimates that we used were obtained from a study from 1998. However, these estimates have been used in recent studies. Fifth, although the cost of acquisition of software was included, it is important to highlight that this cost will depend on the number of patients diagnosed per facility per year. Further research might be needed to assess the cost-effectiveness of MT in the extended window at hospital level. Sixth, given the specifics (including the high costs) of the health care system in the United States, these results are not generalizable to other health care settings, where late MT might be more or less cost-effective.

5.6 CONCLUSIONS

In conclusion, MT with SMC was generally cost-effective in all the subgroups evaluated in the DAWN and DEFUSE 3 trials. Future MT evidence-gathering is needed with a focus on older ages (ie, 80 years) and NIHSS scores of 16 and higher to reduce the uncertainties regarding these findings. More attention should be placed on increasing access to MT rather than on developing subgroup specific guidelines, unless workforce and budget constraints require prioritization.

Additional Contributions

We gratefully acknowledge James Burke, MD (University of Michigan), for his valuable inputs related to this work. We gratefully acknowledge Loic Boussel, PhD, and Philippe Douek, PhD (University Claude Bernard Lyon 1), for proposing the original idea of this article and supporting the related work.

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Supplemental material

eAppendix. Source Data

eFigure 1. Scatterplot of Incremental Costs and Incremental QALYs per Subgroup and Trial

eFigure 2. One-way Sensitivity Analysis Based on the DEFUSE 3 results

eFigure 3. PSA Results, Cost-effectiveness Acceptability Curves Showing the Probability of MT With SMC Being Cost-effective at Different Values of WTP for a QALY, by Subgroups

eTable 1. Short-run Model Input Parameters: Distribution of Patients on the mRS Scale at 3 Months After Initial AIS per Subgroup and Strategy per Trial

eTable 2. Reported Age of Randomized Patients in the DAWN and DEFUSE 3 Trials and Parameterized Age of Patients in our Model

eTable 3. Calculation Methods for the Cost of Software per Ischemic Stroke Patient

eTable 4. Reported Frequencies of Use of Intravenous Thrombolysis in the DAWN and DEFUSE 3 Trials

eTable 5. PSA Results, Monte Carlo Simulations of Incremental Cost and Incremental QALY per Patient with patient of MT With SMC vs SMC alone

eReferences.

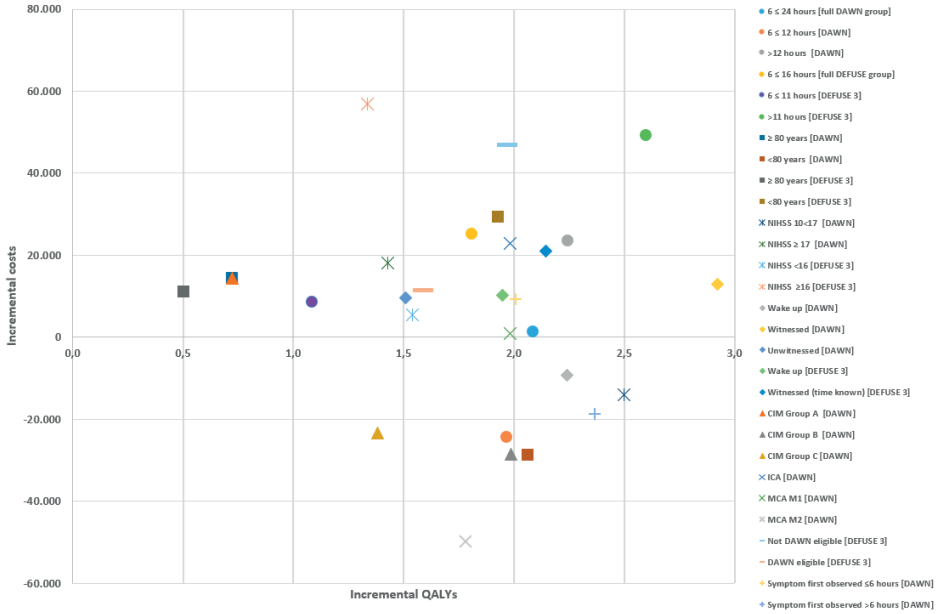
eAppendix. Source Data

In the DAWN trial, patients with an anterior circulation large vessel occlusion, NIHSS >10, and favorable imaging profiles were randomized to either MT (N=107) or medical management (N=99) between 6 to 24 hours after time last known well at centers in the United States, Canada, Europe, and Australia. In DEFUSE 3, patients with anterior circulation large vessel occlusions, NIHSS > 6, and favorable imaging profiles were randomized to MT (N=92) versus medical therapy (N=90) 6 to 16 hours after last known well. Patients were recruited from 38 centers located in the United States.

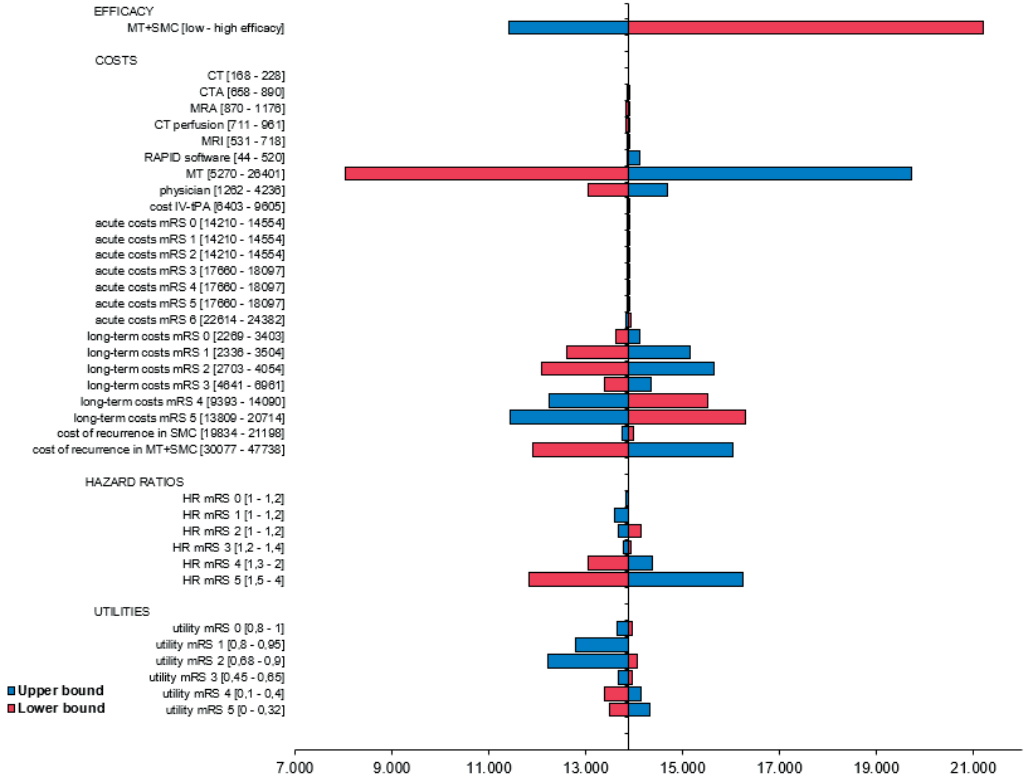
Informed consent was obtained from all participants or their legal representatives. MT was performed with the Trevo device by Stryker in DAWN and with any FDA-approved

device in DEFUSE 3. Intravenous tissue plasminogen activator (IV-tPA) was allowed before randomization, if begun within 4.5 hours from symptom onset.

eFigure 1. Scatterplot of incremental costs and incremental QALYs per subgroup and trial



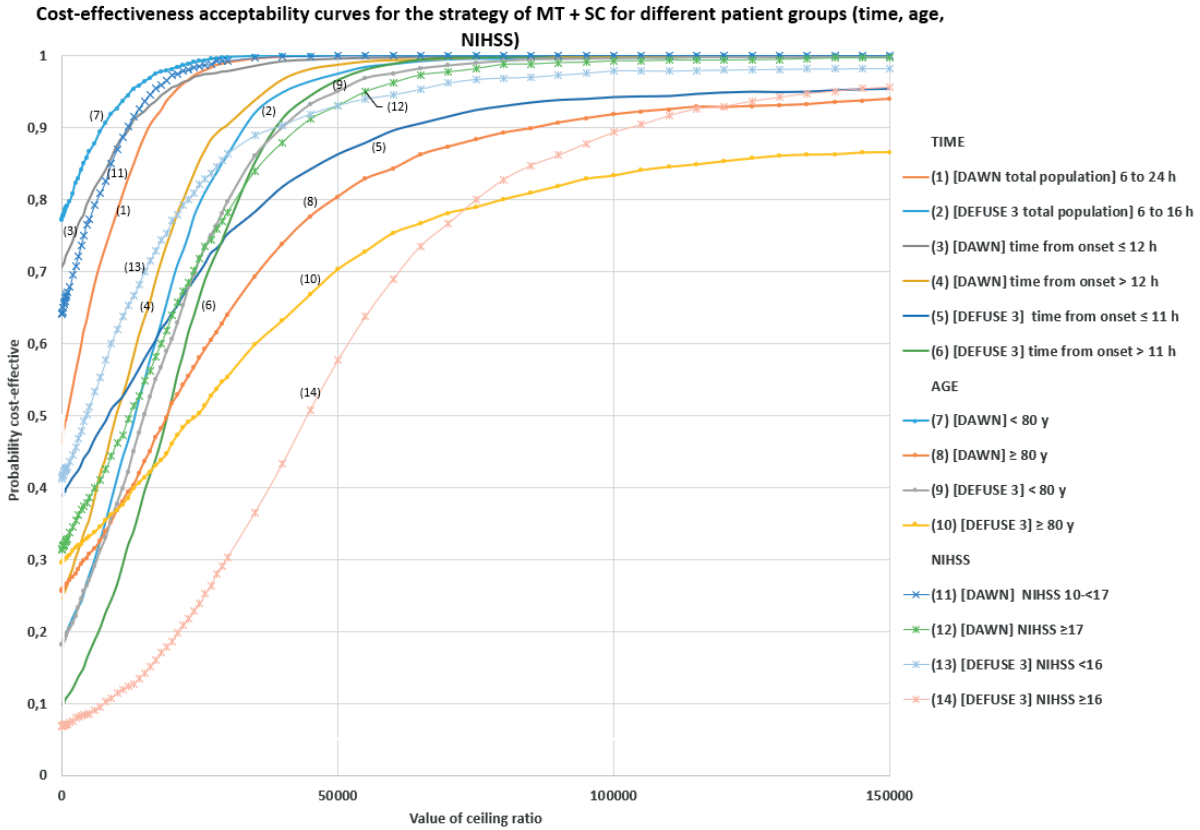
eFigure 2. One-way sensitivity analysis based on the DEFUSE 3 inputs
The plot shows ICER for MT+SMC versus SMC.

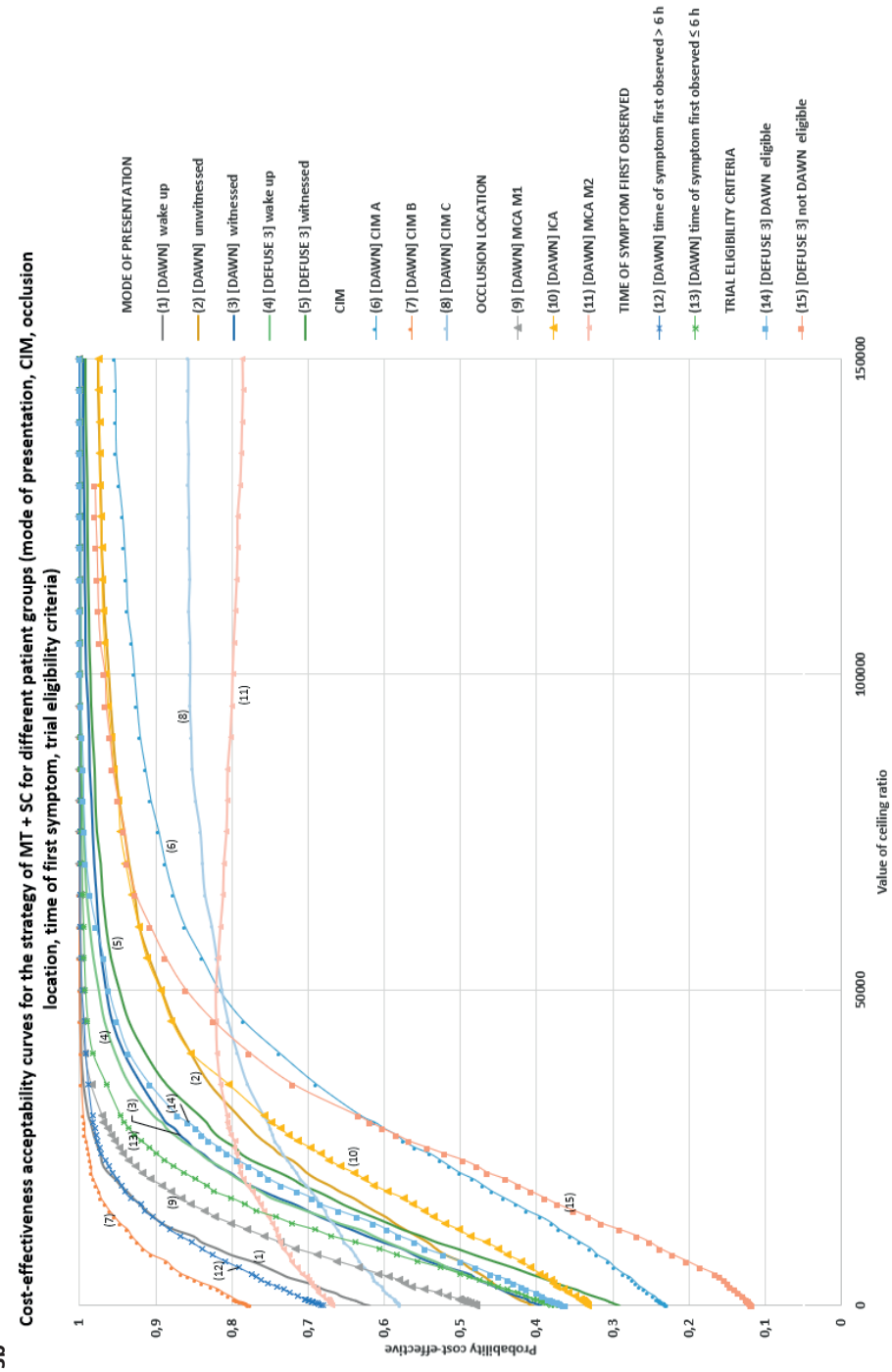


Low and high efficacy of MT+SMC was defined by the following distribution of patients on the mRS score at 3 months:
Low efficacy, by mRS score 0-6 (%): 8.2, 14.2, 16.2, 15, 19.3, 11.2, 16.1
High efficacy, by mRS score 0-6 (%): 11.2, 17.2, 19.2, 15, 17.3, 7.2, 13.2

eFigure 3. PSA results, cost-effectiveness acceptability curves showing the probability of MT with SMC being cost-effective at different values of WTP for a QALY by subgroups (SMC strategy curves not shown)

3a




3b
Cost-effectiveness acceptability curves for the strategy of MT + SC for different patient groups (mode of presentation, CIM, occlusion location, time of first symptom, trial eligibility criteria)
Probability cost-effective
Value of ceiling ratio
0
50000
100000
150000
0,1
0,2
0,3
0,4
0,5
0,6
0,7
0,8
0,9
1
MODE OF PRESENTATION
(1) [DAWN] wake up
(2) [DAWN] unwitnessed
(3) [DAWN] witnessed
(4) [DEFUSE 3] wake up
(5) [DEFUSE 3] witnessed
CIM
(6) [DAWN] CIM A
(7) [DAWN] CIM B
(8) [DAWN] CIM C
OCCLUSION LOCATION
(9) [DAWN] MCA M1
(10) [DAWN] ICA
(11) [DAWN] MCA M2
TIME OF SYMPTOM FIRST OBSERVED
(12) [DAWN] time of symptom first observed > 6 h
(13) [DAWN] time of symptom first observed ≤ 6 h
TRIAL ELIGIBILITY CRITERIA
(14) [DEFUSE 3] DAWN eligible
(15) [DEFUSE 3] not DAWN eligible

eTable 1. Short-run model input parameters: distribution of patients on the mRS scale at 3 months after initial AIS per subgroup and strategy per trial

			DAWN results							
			Distribution at 3 months on the mRS scale							
Criteria	Patient subgroup	Strategy	mRS 0	mRS 1	mRS 2	mRS 3	mRS 4	mRS 5	mRS 6	sample size
Time from stroke onset	**6 ≤ 24 hours (total population)**									
		SMC	4,1%	5,1%	4,1%	16,1%	34,1%	13,6%	22,6%	99
		MT + SMC	9,1%	22,1%	17,1%	13,1%	13,1%	9,5%	15,8%	107
	6 ≤ 12 hours									
		SMC	6,9%	6,9%	5,9%	10,9%	36,9%	12,2%	20,5%	46
		MT + SMC	14%	22%	18%	10%	6%	11,3%	18,8%	50
	>12 hours									
		SMC	1,9%	3,9%	1,9%	20,9%	31,9%	14,9%	24,9%	53
		MT + SMC	5%	23%	16%	16%	19%	7,9%	13,1%	57
Age	**<80 years**									
		SMC	6%	6%	5%	17%	40%	9,8%	16,3%	70
		MT + SMC	8,9%	25,9%	18,9%	11,9%	14,9%	7,4%	12,4%	82
	≥ 80 years									
		SMC	0%	3,8%	0%	13,8%	20,8%	23,1%	38,6%	29
		MT + SMC	12%	12%	8%	16%	8%	16,5%	27,5%	25
NIHSS	**10<17**									
		SMC	9,1%	9,1%	6,1%	18,1%	33,1%	9,1%	15,1%	45
		MT + SMC	16,9%	24,9%	28,9%	7,9%	7,9%	5,1%	8,6%	52
	≥ 17									
		SMC	2%	0%	2%	15%	35%	17,3%	28,8%	54
		MT + SMC	2,1%	20,1%	5,1%	18,1%	18,1%	13,6%	22,6%	55
Mode of presentation	**Wake up**									
		SMC	5%	4%	2%	17%	38%	12,8%	21,3%	47
		MT + SMC	11%	22%	16%	15%	12%	9%	15%	67
	Unwitnessed									
		SMC	3%	5%	5%	18%	29%	15%	25%	38
		MT + SMC	7%	24%	10%	7%	17%	13,1%	21,9%	29
	Witnessed									
		SMC	7%	7%	7%	7%	36%	13,5%	22,5%	14
		MT + SMC	9%	18%	37%	18%	9%	3,4%	5,6%	11

eTable 1. Short-run model input parameters: distribution of patients on the mRS scale at 3 months after initial AIS per subgroup and strategy per trial (*continued*)

Criteria	Patient subgroup	Strategy	DAWN results Distribution at 3 months on the mRS scale mRS 0	mRS 1	mRS 2	mRS 3	mRS 4	mRS 5	mRS 6	sample size
Clinical Infarct Mismatch (CIM)	**CIM Group A**									
		SMC	0%	3,8%	0%	13,8%	20,8%	23,1%	38,6%	29
		MT + SMC	12%	12%	8%	16%	8%	16,5%	27,5%	25
	CIM Group B									
		SMC	7%	7%	6%	20%	39%	7,9%	13,1%	61
		MT + SMC	10%	26%	21%	12%	15%	6%	10%	73
	CIM Group C									
		SMC	0%	0%	0%	0%	44%	21%	35%	9
		MT + SMC	0%	22,2%	11,2%	11,2%	11,2%	16,7%	27,7%	9
Occlusion location	**Internal Carotid Artery (ICA)**									
		SMC	0%	0%	0%	21%	21%	21,8%	36,3%	19
		MT + SMC	4,9%	26,9%	13,9%	13,9%	4,9%	13,4%	22,4%	22
	Middle Cerebral Artery M1 Segment									
		SMC	5%	7%	5%	14%	38%	11,6%	19,4%	77
		MT + SMC	10,9%	20,9%	17,9%	12,9%	15,9%	8,1%	13,6%	83
	Middle Cerebral Artery M2 Segment									
		SMC	0%	0%	0%	33,3%	33,3%	12,7%	20,9%	3
		MT + SMC	50%	0%	0%	0%	0%	18,8%	31,3%	2
Time of symptom first observed	**Symptom First Observed ≤ 6 hours**									
		SMC	2%	6%	5%	20%	32%	13,1%	21,9%	54
		MT + SMC	10%	23%	13%	14%	16%	9%	15%	74
	Symptom First Observed > 6 hours									
		SMC	7%	4%	2%	11%	38%	14,3%	23,8%	45
		MT + SMC	9,1%	21,1%	24,1%	12,1%	6,1%	10,3%	17%	33
Time from stroke onset	**6 ≤16 hours (total population)**									
		SMC	7,9%	3,9%	3,9%	15,9%	26,9%	15,9%	25,9%	90
		MT + SMC	10,1%	16,1%	18,1%	15,1%	18,1%	8,1%	14,1%	92
	6 ≤11 hours									
		SMC	11,9%	5,9%	5,9%	15,9%	24,9%	17,9%	17,9%	51
		MT + SMC	12,3%	14,3%	16,3%	12,3%	20,3%	8,3%	16,3%	49
	>11 hours									
		SMC	2,9%	2,9%	2,9%	14,9%	27,9%	12,9%	35,9%	39
		MT + SMC	6,9%	18,9%	20,9%	18,9%	15,9%	6,9%	11,9%	43

eTable 1. Short-run model input parameters: distribution of patients on the mRS scale at 3 months after initial AIS per subgroup and strategy per trial (*continued*)

Criteria		DEFUSE 3 results							
		Distribution at 3 months on the mRS scale							
	Patient subgroup	Strategy	mRS 0	mRS 1	mRS 2	mRS 3	mRS 4	mRS 5	mRS 6	sample size
Age	**<80 years**									
		SMC	10,9%	5,9%	4,9%	19,9%	23,9%	14,9%	19,9%	66
		MT + SMC	12,7%	15,7%	22,7%	15,7%	18,7%	5,7%	8,7%	70
	≥ 80 years									
		SMC	0%	0%	4%	4%	33%	17%	42%	24
		MT + SMC	0%	17,8%	4,8%	13,8%	17,8%	13,8%	31,8%	22
NIHSS	**<16**									
		SMC	15,9%	8,9%	8,9%	21,9%	17,9%	15,9%	10,9%	45
		MT + SMC	18,9%	22,9%	20,9%	11,9%	11,9%	6,9%	6,9%	43
	≥16									
		SMC	0%	0%	0%	8,8%	35,8%	15,8%	39,8%	45
		MT + SMC	2,3%	10,3%	16,3%	18,3%	24,3%	8,3%	20,3%	49
Mode of presentation	**Wake up**									
		SMC	5%	0%	2%	17%	26%	19%	31%	42
		MT + SMC	8,3%	16,3%	18,3%	14,3%	16,3%	6,3%	20,3%	49
	Time known									
		SMC	8,9%	5,9%	8,9%	10,9%	28,9%	16,9%	19,9%	35
		MT + SMC	16%	19%	23%	10%	13%	13%	6%	31
Trial eligibility criteria	**Not DAWN eligible**									
		SMC	8,9%	5,9%	8,9%	8,9%	23,9%	11,9%	31,9%	34
		MT + SMC	11%	19%	25%	6%	17%	8%	14%	36
	DAWN eligible									
		SMC	6,9%	3,9%	1,9%	19,9%	28,9%	17,9%	20,9%	56
		MT + SMC	9,1%	14,1%	14,1%	21,1%	20,1%	7,1%	14,1%	56

Clinical infarct mismatch: mismatch between the severity of the clinical deficit and the infarct volume defined according to the following groups:
Group A: age ≥80, NIHSS ≥10, infarct volume <21ml
Group B: age< 80, NIHSS ≥10, infarct volume <31ml
Group C: age< 80, NIHSS ≥20, infarct volume <31-51ml
Time of symptom first observed to randomization
ICA: Internal carotid artery
MCA M1: middle cerebral artery M1 segment
NIHSS: National Institutes of Health Stroke Scale

eTable 2. Reported age of randomized patients in the DAWN and DEFUSE 3 trials and parameterized age of patients in our model

Total study population	**SMC + MT**		**SMC alone**	
	Data from the trial	Data used in our model*	Data from the trial	Data used in our model*
DAWN	69.4 (SD=14.1)	69	70.7 (SD=13.2)	71
DEFUSE 3	70	70	71	71
Age ≥80 year	**SMC + MT**		**SMC alone**	
	Data from the trial	Data used in our model (mean age of the patients ≥80)*	Data from the trial	Data used in our model (mean age of the patients ≥80)*
DAWN	23%	86.3 rounded to 86	29%	86.2 rounded to 86
DEFUSE 3	23.9%**	86.6 rounded to 87	26.6%**	86
Age <80 year	**SMC + MT**		**SMC alone**	
	Data from the trial	Data used in our model (mean age of the patients <80)*	Data from the trial	Data used in our model (mean age of the patients <80)*
DAWN	77%	65.4 rounded to 66	71%	66.6 rounded to 67
DEFUSE 3	76.1%**	65.7 rounded to 66	73.3%**	66.7 rounded to 67

*estimated assuming a normal distribution around the mean age of the full randomized population (tool: http://davidmlane.com/hyperstat/z_table.html)

** calculated from the data provided in the DAWN and DEFUSE 3 studies

eTable 3. Calculations methods for the cost of software per ischemic stroke patient

	Mean (range)	Comments	Reference
Thrombectomy-capable centers	53	Minimum 15 patients/year	The Joint Commission Website [1]
Comprehensive stroke centers (CSC)	194	-	
Annual stroke patients	795,000		[2]
Annual ischemic stroke patients (87%)	691,650		
Annual ischemic stroke patients in the 6-23-hour onset-to-door window (those likely to receive advanced-imaging and to require the use of RAPID software)	~10.5%*691,650 = 72,623	Of all ischemic stroke patients: 3.0% presented >24 hours 53.0% did not have exact time of onset documented Of the 44% remaining, 25.4% were in the 6 to 24-hour onset-to-door window. Assuming linearity, this is 24% in the 6-23-hour window. (1 hour is assumed between arrival at hospital and imaging assessment). 44%*24%=10.5% (probably an overestimate if there are other contraindications or obstacles to MT for patients within this time window)	[3]
Annual ischemic stroke patients in the 6-23-hour window/stroke center	72,623 / 247 = 294 (100 – 400)	Range assumed	
	Cost (range)		
RAPID software Annual cost per facility	$26,250 ($17,500 -52,000)	depending on configuration (1 scanner or unlimited)	feedback from RAPIDAI (VP sales contact) and from one hospital in the US (for the upper bound)
RAPID software Cost/ischemic patient (6-24-hour window)/ scan	$89 ($44 – 520)		

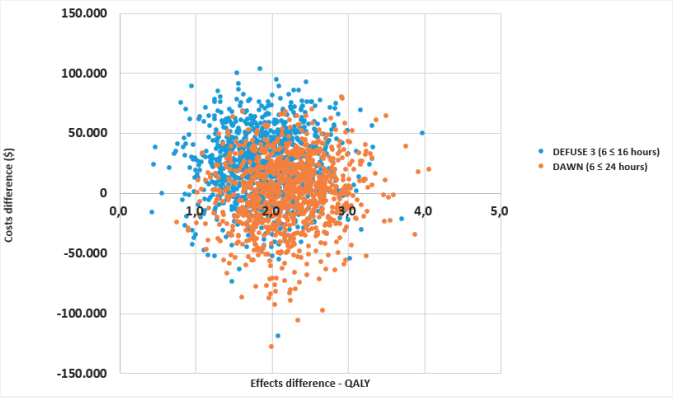
eTable 4. Reported frequencies of use of intravenous thrombolysis in the DAWN and DEFUSE 3 trials

	DAWN	DEFUSE 3
Intervention (MT+SMC)	5%	11%
Control (SMC alone)	13%	9%

eTable 5. PSA results - Monte Carlo simulations of incremental cost and incremental QALY per AIS patient of MT+SMC (versus SMC alone)
Probabilistic sensitivity analysis per patient group and all subgroups of the DAWN and DEFUSE 3 trials.

TIME FROM SYMPTOM ONSET

when performed within 6 to 24 hours (DAWN) and when performed within 6 to 16 hours (DEFUSE 3) (total population of both studies)



TIME FROM SYMPTOM ONSET

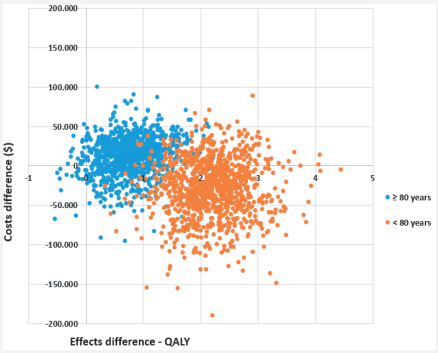
when performed within 12 hours compared to beyond 12 hours (DAWN)

when performed within 11 hours compared to beyond 11 hours (DEFUSE 3)

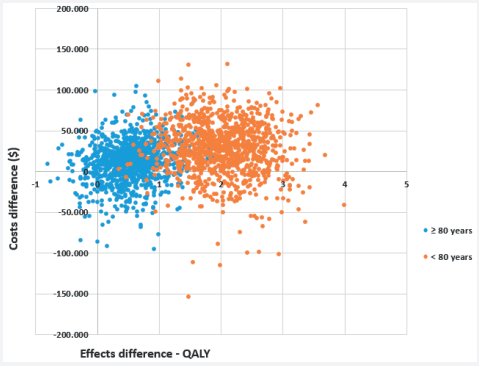
eTable 5. PSA results - Monte Carlo simulations of incremental cost and incremental QALY per AIS patient of MT+SMC (versus SMC alone) *(contined)*

AGE
when performed within or beyond 80 years of age

DAWN

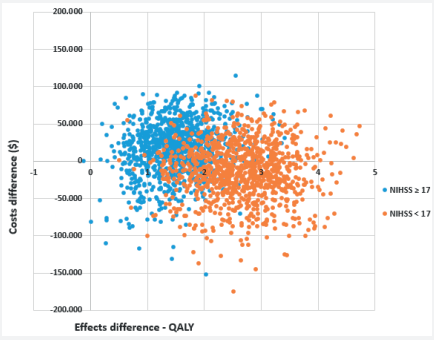


DEFUSE 3



NIHSS

when performed in patients with a baseline NIHSS of 10 to 17 versus beyond (DAWN)



when performed in patients with a baseline NIHSS of 16 or less versus beyond (DEFUSE 3)

MODE OF PRESENTATION

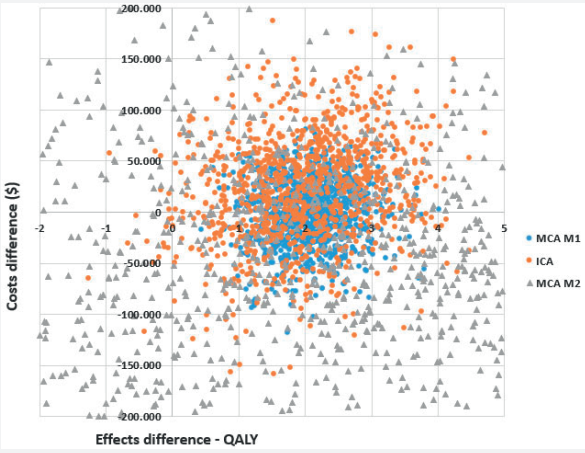
when performed in patients with wake-up stroke versus unwitnessed stroke (DAWN)

when performed in patients with wake-up stroke versus witnessed stroke (DEFUSE 3)

eTable 5. PSA results - Monte Carlo simulations of incremental cost and incremental QALY per AIS patient of MT+SMC (versus SMC alone) *(contined)*

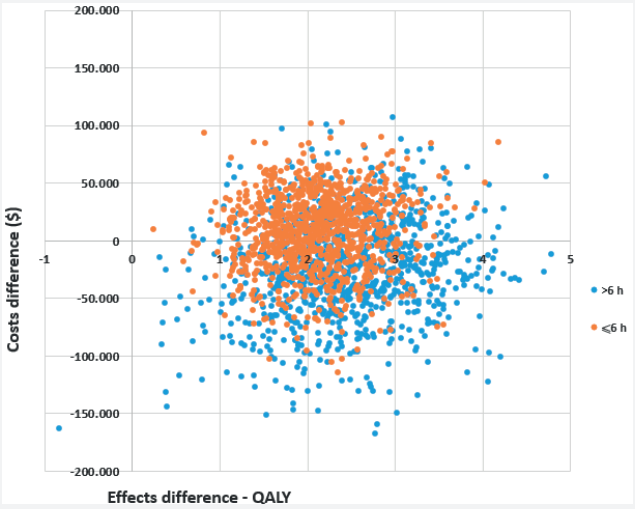
CLINICAL INFARCT MISMATCH (DAWN)
when performed in patients with a specific infarct mismatch versus another one

OCCLUSION LOCATION (DAWN)
when performed in patients with MCA M1 occlusion versus ICA



eTable 5. PSA results - Monte Carlo simulations of incremental cost and incremental QALY per AIS patient of MT+SMC (versus SMC alone) *(contined)*

TIME OF SYMPTOM FIRST OBSERVED (DAWN)
when performed within or beyond 6 hours of symptom first observed



TRIAL ELIGIBILITY CRITERIA (DEFUSE 3)
when performed in patients eligible to the DAWN trial versus those non eligible

References

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2. Mozaffarian D, Benjamin EJ, Go AS, et al. Executive Summary: Heart Disease and Stroke Statistics—2016 Update. A Report From the American Heart Association. Circulation 2016;133:e38–e360.795,000.
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6

Validity of transferring a cost-effectiveness model across countries: the case of advanced imaging + late thrombectomy in stroke care UNDER EMBARGO

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Submitted

7

European survey on acute coronary syndrome diagnosis and revascularisation treatment: Assessing differences in reported clinical practice with a focus on strategies for specific patient cases

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Abstract

Rationale, Aims, and Objectives

While different imaging and treatment options are available in acute coronary syndrome (ACS) care, there is a lack of data regarding their use across Europe. We examined the diagnostic and treatment strategies in patients with known or suspected ACS as reported by physicians and identified variations in responses across European countries and geographical areas.

Method

A web-based clinician survey focusing on ACS imaging and revascularization treatments was circulated through email distribution lists and websites of European professional societies in the field of cardiology. We collected information on respondents' clinical setting and specialty. Reported percentages of patients receiving imaging or treatment modalities and percentages of clinicians reporting to use modalities in a range of clinical scenarios were analyzed. Statistical comparisons were performed.

Results

In total, 69 responses were received (Sweden [n = 20], United Kingdom [n = 16], Northern/Western Europe [n = 17], Southern Europe [n = 9], and Central Europe [n = 7]). Considerable variations between geographical areas were seen in terms of reported diagnostic modalities and treatment strategies. For example, when presented with the scenario of a theoretical 45-year-old smoking female with a suspected ACS, 56% of UK clinicians reported to use coronary computed tomography angiography, compared to only 10% of Swedish clinicians (P = .002). Large variations were observed regarding the reported use of fractional flow reserve by physicians for non-culprit lesions during invasive management of myocardial infarction patients (44% in Sweden, 31% in the United Kingdom, and 30% in Northern/Western Europe vs non-use in Central and Southern Europe).

Conclusions

In this survey, respondents reported different diagnostic and treatment strategies in ACS care. These variations seem to have geographic components. Larger studies or real world data are needed to verify these observations and investigate their causes. More research is needed to compare the quality and efficiency of ACS care across countries and explore pathways for improvement.

7.1 INTRODUCTION

Acute coronary syndrome (ACS) refers to conditions where the blood supplied to the heart muscle gets suddenly blocked leading to the death of cells in the heart tissues. In patients with suspected ACS, several imaging or functional testing modalities may be used to establish the diagnosis and to identify patients who should undergo myocardial revascularization. As different imaging and treatment options are currently available in the field, this variety might leave room for clinical practice variation at the European level.

Evidence suggests differences in ACS care and outcomes within Europe [1]. However, variations in clinical practice and outcomes in ACS care have mainly been analyzed at a national level, providing information about the relative patterns and performance of different hospitals within individual countries [2]. Although this information is crucial to assess the performance of hospitals and identify inequalities in care at the national level, between-country comparisons have received little attention and would provide a complementary opportunity for learning from foreign health care systems and improving national performances [2]. Furthermore, given the lack of reliable data, establishing the status of the use of cardiovascular imaging in Europe has been a priority for influential European associations in the field [3].

While both surveys and registries are needed to verify whether clinical practice is in line with guidelines [4], surveys offer the advantage to present specific clinical cases and obtain detailed information about diagnostic and management strategies.

In this context, we developed and used a web-based clinician survey to examine the diagnostic and treatment strategies reported by respondents and to identify potential variations in responses between countries or geographical areas within Europe. The focus was made on diagnostic tests (including coronary imaging and functional assessment) and revascularization treatment, in a range of clinical scenarios encompassing patients with known or suspected ACS.

7.2 METHODS

7.2.1 Study design

In order to assess clinical practice in ACS in Europe, we conducted an online clinician survey. The survey questions were formulated based on expert opinion and feedback collected from a European expert panel, which included five cardiologists and three radiologists.

A pilot phase was conducted before the survey was launched in March 2017. The survey was conducted using the online software "Google form" and was made available online. The target population for dissemination included non-invasive and interventional cardiologists, radiologists, and emergency physicians (including those completing their specialization).

No financial incentive was offered to participants and survey completion was voluntary. An ethics committee (EMC Rotterdam) reviewed the protocol and survey questions and concluded that this work was not subject to the Dutch law of medical research (WMO).

7.2.2 Structure

A closed and structured format in English was chosen to enable clinicians to select their responses among multiple predefined choices. First, an introduction provided the framework of the study and was followed by general questions regarding the respondents' work setting. Subsequently, respondents were asked about the diagnostic workup and the proportions of high-risk and low- to intermediate-risk patients suspected with ACS who would receive different imaging modalities in the respondent's practice setting. Section 5 contained questions about the treatments used for ST-elevation myocardial infarction (STEMI) and non-ST segment elevation myocardial infarction (NSTEMI) patients while Section 6 focused on follow-up imaging. Questions related to specific patient cases and clinical scenarios were disseminated throughout the survey and are summarized in Table 7.1. The survey questions can be found in Supporting Information. A pilot-test phase was conducted after which the number of questions was reduced.

7.2.3 Dissemination

The online survey link was circulated through email distribution lists and websites of national and European professional societies. The Swedish Society of Cardiology, the British Society of Cardiovascular Imaging, and the Radcliffe Cardiology group invited their members to participate in the survey through personal emails. The survey was circulated via the website of the Bulgarian Society of Cardiology, the Czech Nuclear Medicine Society, the European Society of Cardiovascular Radiology, and the Hungarian

Society of Cardiology, which complemented this action with an announcement in their newsletter.

Table 7.1 Clinical scenarios as defined in the survey

Patient case number	Patient case	Procedure surveyed
1	45-year-old female woman suspected with ACS, admitted in the emergency department. She had no cardiovascular risk factor except for smoking during 20 years. She presents with an atypical chest pain, her ECG is normal and her troponin result is low.	Further examination
2	65-year-old NSTEMI patient who received PCI of the culprit lesion and presents a relatively good clinical status	Strategy for dealing with suspected non-culprit lesions
3	Patient over 50 y-o, admitted to the health centre with chest pain and an ACS has been ruled out	Usual diagnostic strategy after an ACS was ruled out

Abbreviations: ACS, acute coronary syndrome; ECG, electrocardiogram; NSTEMI, non-ST segment elevation myocardial infarction; PCI, percutaneous coronary intervention.

7.2.4 Statistical analysis

Reported percentages of patients receiving imaging or treatment modalities and percentages of respondents reporting to use different invasive or non-invasive diagnostic tests or treatments were extracted from the clinicians' responses. Non-invasive diagnostic tests comprise anatomical imaging such as coronary computed tomography angiography (CTA) or functional (or stress) tests, including exercise electrocardiogram (ECG), stress echocardiography, and scintigraphic or magnetic resonance (MR) perfusion imaging. In ACS care, functional imaging is used to assess the haemodynamic characteristics of the heart. Invasive assessments require insertion of cardiac catheters and include invasive coronary angiography and fractional flow reserve (FFR) assessment during an interventional procedure.

Mean percentages were calculated for two countries (Sweden and the United Kingdom) and three clusters of countries (Central Europe, Northern/Western Europe, and Southern Europe) that were created based on the geographic location of the respondents and expected commonalities in their health care system. Given the breakdown of participants per country, Sweden and the United Kingdom were extracted from the Northern/Western Europe cluster and isolated for more detailed analyses. Our statistical analyses rely on the assumption that respondents can be considered to be independent observations. Based on background information of the hospital (city, academic centre, and number of MI diagnosed), the maximum possible number of respondents coming from

the same centre is very low, which means that the potential influence of this possibility on the results is low.

The 95% confidence intervals (CIs) surrounding the mean estimates were computed using bootstrapping [5]. This involved randomly resampling the original samples with replacement 500 times, which corresponded to the number of replications needed to ensure stability and accuracy. Each bootstrapped sample yielded a bootstrap statistic (eg, mean frequency). The bootstrap distribution was computed from the 500 bootstrap statistics, per geographic area. Between-country and between-cluster comparisons of imaging and treatments were conducted using one-way ANOVA tests in SPSS (version 23). Statistical significance of the results was tested using a .05 level.

7.2.5 General background regarding the availability and use of imaging modalities in the European Union

Previous studies reported considerable variation in the availability and use of imaging equipment in the European Union (EU). In 2015, Luxembourg recorded the highest number of angiography units per capita, followed by Italy and Sweden (Table 7.2) [6]. Germany and Italy reported more than 2.8 magnetic resonance imaging (MRI) units per 100 000 inhabitants, in contrast to 0.4 MRI units per 100 000 inhabitants in Hungary. In 2016, Luxembourg and France had the highest number of CT scans per capita in the EU (21 100 scans and 20 400 scans per 100 000 inhabitants). Furthermore, while Sweden, and Northern Europe in general, are known for their early adoption of medical technologies, Eastern European countries tend to be late adopters [7,8].

Table 7.2 Availability and use of imaging equipment in a set of selected EU countries [6]

Per 100 000 inhabitants	Availability			Use	
	Angiography units (2015)	CT scanners (2016)	MRI units (2016)	CT scanners (2016)	MRI units (2016)
France	0.7	1.7	1.4	20 439	11 385
Germany	1.1	3.5	3.5	14 310 [a]	13 616 [a]
Hungary	0.6	0.9	0.4	11 619	4 224
Italy	1.4	1.3 [a]	2.8 [a]	8 129	6 710
Luxembourg	1.6	1.7	1.2	21 064	8 340
Spain	0.6	1.8	1.6	10 870	8 245
Sweden	1.3	2.2	1.6	NA	NA
UK	NA	1	0.7	8 470	5 676

Abbreviations: CT, computed tomography; MRI, magnetic resonance imaging.
a 2015.

7.3 RESULTS

We received responses from 74 clinicians. Of those, four non-European clinicians and one non-interpretable response set were excluded from the analysis. Among the 69 remaining respondents, 20 were from Sweden, 16 from the United Kingdom, 7 from Central Europe, 17 from Northern/Western Europe, and 9 from Southern Europe. Given that the survey was distributed by national professional societies, it was not possible to calculate the response rate. We acknowledge the fact that the response rate might be small. Details about the respondents' characteristics and work environment can be found in Table 7.3.

Table 7.3 Respondents' characteristics

	Number	%
Number of respondents	69	100
Countries and clusters		
Sweden	20	29%
UK	16	23%
Central Europe (Czech Republic, Hungary, Romania, Serbia)	7	10%
Northern and Western Europe (Finland, France, Germany, Ireland, Luxembourg, Netherlands)	17	25%
Southern Europe (Greece, Italy, Spain, Macedonia)	9	13%
Specialty		
Cardiologist	42	61%
Cardiologist and emergency physician	1	1%
Cardiologist and PCI operator	17	25%
Cardiologist, PCI operator and emergency physician	1	1%
Emergency physician	1	1%
PCI operator	2	3%
Radiologist	5	7%
Financing system		
Public	64	93%
Private	5	7%
Teaching category		
Academic hospital	48	70%
Non-academic hospital	21	30%

Abbreviation: PCI, percutaneous coronary intervention.

7.3.1 Initial diagnostic workup

On the basis of all answers, ECG combined with biochemical tests was reported as the mainstay of the first-line diagnostic workup for both high-risk patients (79%; 95% CI: 70%, 87%) and low- to intermediate-risk patients (68%; 95% CI: 58%, 78%) admitted to a health centre in Europe with chest pain and suspected ACS. Across the different investigated areas, non-invasive test appears to respondents to play a greater role to establish or rule out the diagnosis of an ACS in low- to intermediate-risk patients than in high-risk

patients. Indeed, while an average of 64% of the low- to intermediate-risk patients were reported to receive non-invasive imaging (with ECG plus biochemical tests, with ECG only and with biochemical tests only), only 48% of the high-risk patients were reported to receive it (see Figure S1).

7.3.2 Diagnosis of a low risk patient

The first patient case described a 45-year-old woman suspected with ACS admitted in the emergency department with no cardiovascular risk factors except for smoking for 20 years, atypical chest pain, a normal ECG, and a low troponin result. The respondents were asked to indicate what further investigations they would perform. In this hypothetical clinical case, the vast majority of the clinicians responded they would opt for a combination of coronary CTA and/or echocardiogram and/or stress tests (see Figure 7.1). The combination of tests reported by the respondents can be found in Figure S2. On the basis of the responses, stress tests (including treadmill, scintigram, stress echocardiogram, or stress MRI) would be obtained by 43% to 65% of the respondents in each of the five investigated areas. The use of coronary CTA was reported to be the highest among UK respondents (56%) and lowest among Swedish respondents (10%) (P = .002). Swedish and Southern Europe respondents strongly favoured stress tests in this context.

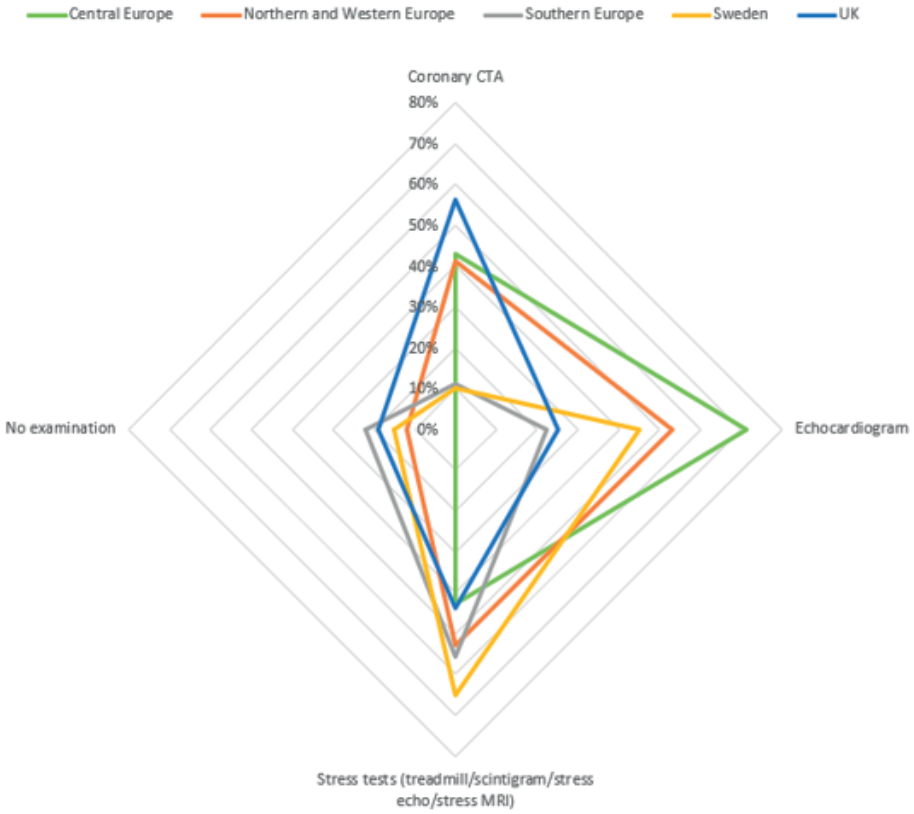
Significantly more UK respondents (56%) than Swedish respondents (10%) reported they would use coronary CTA (P = .002). Large variations were also observed regarding the use of echocardiogram: while 71% of the respondents from Central Europe reported they would perform an echocardiogram, this was only 22% in Southern Europe and 25% in the United Kingdom. Interestingly, throughout the different geographic areas, a varying proportion of respondents (0%-22%) reported they would not perform any further examination.

7.3.3 Imaging modality guiding treatment decision for patients with a high probability of ACS after biochemical tests

Overall, European respondents reported that an average of 60% of their patients presenting with a high probability of ACS after biochemical tests receive echocardiogram (see Figure S3). Furthermore, European respondents reported that an estimated 54% of their patients receive invasive coronary angiography without FFR compared to 37% receiving invasive coronary angiography with FFR.

Southern European respondents reported the lowest frequencies of FFR combined with invasive coronary angiography. While UK respondents reported using coronary CTA for an average of 14% of their patients, Swedish respondents reported using it for only 3% (P = .04).

Figure 7.1 Percentages of clinicians reporting to use different examinations in the diagnosis of a low risk patient (patient case 1)



Other modalities reported:
(percentages of respondents per geographical area)

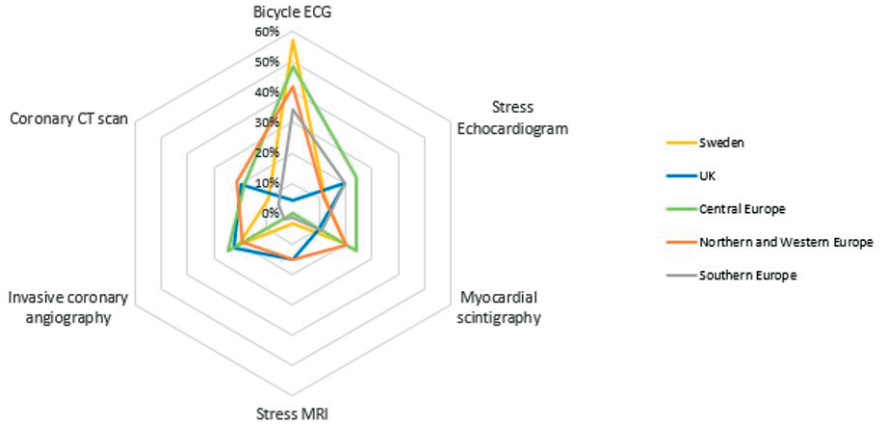
	Invasive coronary	MRI	Bicyclet test	D-dimer	Xray Chest	Pulmonary CTA
Central Europe						14%
Northern and Western Europe	12%	6%		6%	6%	
Southern Europe	11%					
Sweden			5%			
UK						

7.3.4 Diagnosis after ruling out ACS

Figure 7.2 shows the frequencies of diagnostic tests for patients over 50 years of age admitted with chest pain and after an ACS was ruled out, based on the proportion of patients per test reported by each respondent (patient case 3). For these typical patients, UK respondents reported using bicycle ECG less often than the other European respondents. The difference between British and Swedish respondents was statistically significant (4.5% vs 57%; P = .00). Interestingly, UK respondents appear to be almost equally

divided between performing stress echocardiogram, coronary CT scan, and invasive coronary angiography, with frequency rates close to 20% for each test. UK respondents, together with Northern/Western Europe respondents, reported the highest frequencies of stress MRI: 15% and 15.5%, respectively. On average, English respondents estimated that 15% of their patients matching the hypothetical case 3 description receive stress MRI, which means that this imaging modality is significantly more often reported in the United Kingdom than in Sweden, Central Europe, and Southern Europe ($P < .05$), in the described context. The reported use of stress MRI also appears to be significantly greater in London than in other UK cities ($P < .01$).

Figure 7.2 Reported percentages of patients receiving different diagnostic strategies after an ACS was ruled out (patient case 3). ACS, acute coronary syndrome



7.3.5 Average time between diagnosing a NSTEMI patient and performing invasive coronary angiography

The reported time between diagnosing an NSTEMI patient and performing invasive coronary angiography appear to vary substantially between and within the investigated areas. While 18% of the whole group of respondents (12/69) estimated an average time of 24 hours between diagnosis and invasive coronary angiography, 52% (36/69) of these respondents reported a delay of more than 24 hours. Of these 36 respondents, 13 estimated a delay of at least 72 hours, hence a total of 19% (13/69) of the whole group. Interestingly, while 45% (9/20) of the Swedish respondents reported performing coronary angiography within 24 hours, all UK respondents estimated this delay to be greater than 24 hours.

7.3.6 Reperfusion treatment method for patients presenting with a STEMI and revascularization treatment method for patients presenting with a primary NSTEMI

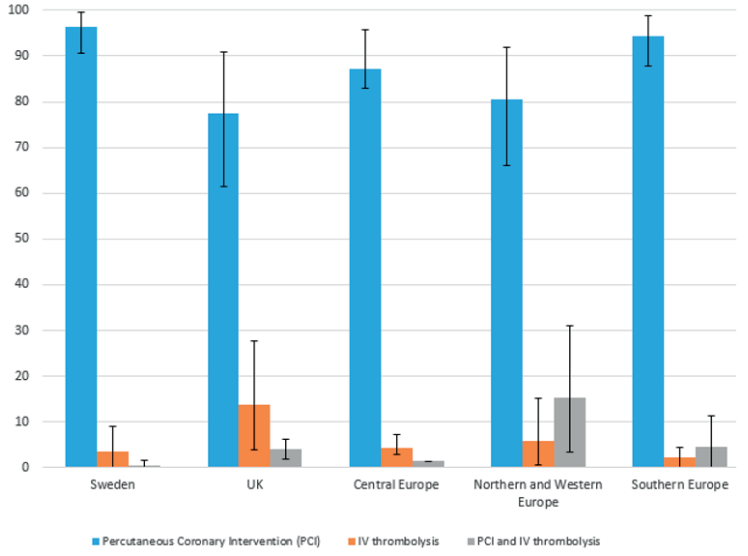
Figure 7.3 shows the reported frequencies of reperfusion treatments and revascularization treatments given to STEMI patients (A) and NSTEMI patients (B), respectively, who were not contra-indicated for any treatment. Percutaneous coronary intervention (PCI) was reported as the primary treatment modality for both STEMI and NSTEMI patients. This was the case in all geographical areas, although the actual percentage varied somewhat between geographical areas, with ranges of 77% to 96% for STEMI patients and 67% to 91% for NSTEMI patients. For the two categories of patients, the lowest rates of PCI were reported in the United Kingdom. The UK respondents also reported the highest rate of intravenous thrombolysis, with nearly 14% of their STEMI patients receiving it, compared to an average of 2% to 6% reported in the other geographic areas. Regarding the NSTEMI group, UK respondents reported the highest rate of coronary artery bypass grafting (CABG) (19%) across the investigated areas.

7.3.7 Treatment of non-culprit lesions

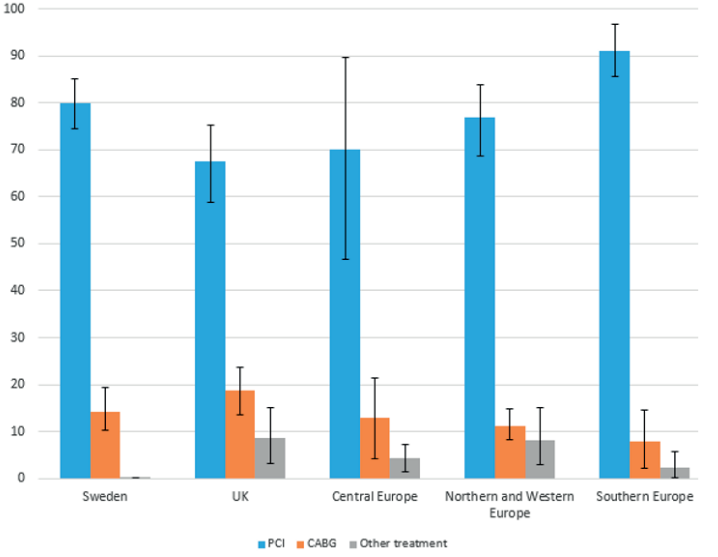
In a second patient case, respondents were asked about how they would treat suspected non-culprit lesions in a 65-year-old NSTEMI patient presenting with a relatively good clinical status following the PCI of the culprit lesion. For this typical patient, slightly more than one-quarter of the whole group of European respondents (19/69 = 28%) reported they would opt for conservative management with PCI only in the case of symptoms or reversible ischemia on stress tests (see Figure 7.4). Despite this trend, large variations are observed between responses across geographical areas: while this strategy was chosen by 56% and 57% of the respondents in Southern Europe and Central Europe, respectively, it was selected by only 16% to 25% of the respondents in the United Kingdom, Sweden, and Northern/Western Europe. The strategy of FFR was chosen by 26% (18/69) of the total group: 16% (11/69) of the whole European respondents opted for an immediate FFR-guided PCI during index catheterization, 9% (6/69) for a staged FFR-guided PCI during index hospitalization, and one respondent opted for a staged FFR-guided PCI between 4 and 8 weeks. Among the respondents reporting PCI, the strategy of immediate PCI was most prevalent in the United Kingdom and Sweden (67% and 36%, respectively) (Figure 7.4B). No clinician from Southern Europe reported FFR-guided PCI or immediate PCI in case of non-culprit lesions (Figure 7.4B).

Figure 7.3 A, Reported percentages of STEMI patients receiving different reperfusion treatments. B, Reported percentages of NSTEMI patients receiving different revascularization treatments.

3A

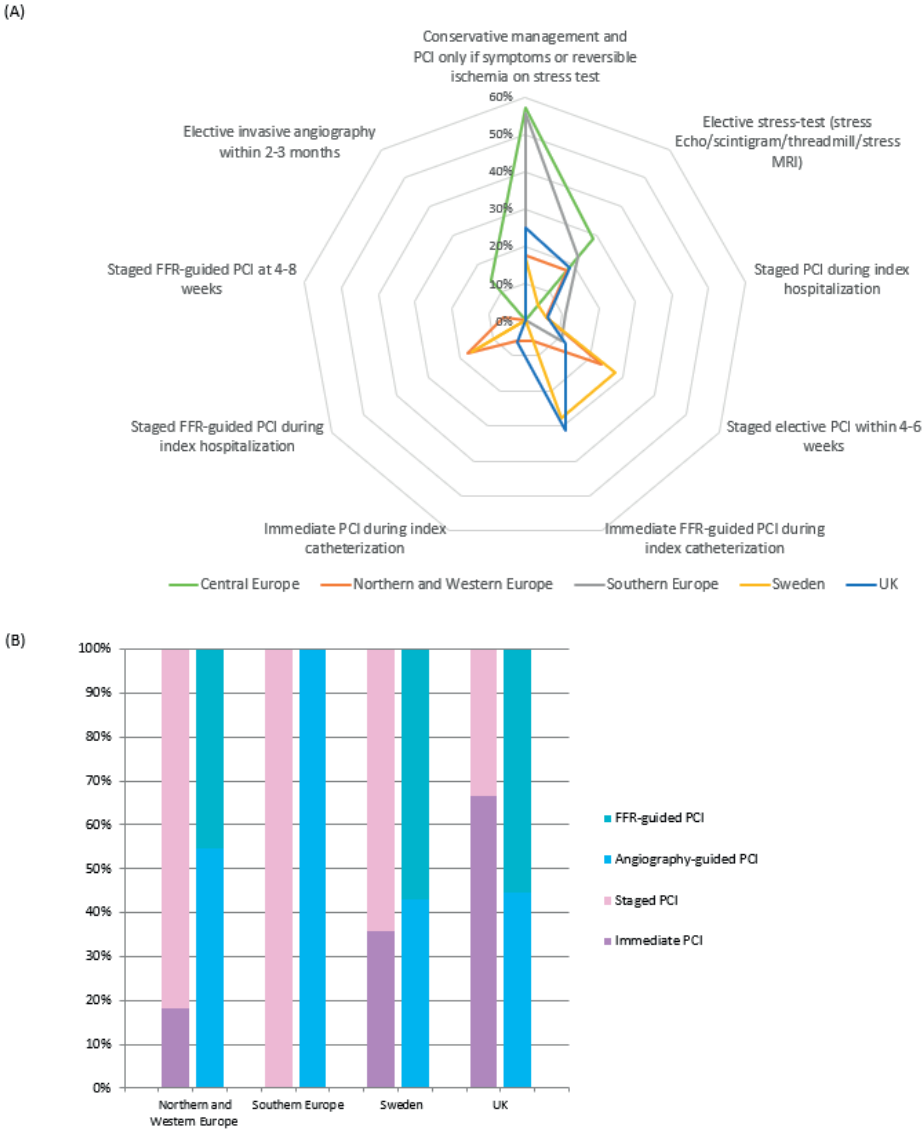


3B



NSTEMI, non-ST segment elevation myocardial infarction; STEMI, ST-elevation myocardial infarction

Figure 7.4. A, Percentages of clinicians reporting their most common strategy in treating non-culprit lesions (patient case 2). B, Percentages of clinicians reporting different approaches when performing PCI of the non-culprit lesion (patient case 2). PCI, percutaneous coronary intervention



Totals per country do not sum up to 100% due to respondents who reported a "I do not know" answer.

7.4 DISCUSSION

To the best of our knowledge, this study presents the first online survey aimed at describing and analyzing reported diagnostic and treatment practices in ACS care across

European regions and countries. This study also provides detailed data related to a range of clinical scenarios that focus on strategies for specific patients.

Considerable variations in the respondents' answers were observed in both the diagnostic and treatment phases of patients with known or suspected ACS. In addition, comparative analyses revealed significant differences between the responses from Swedish and UK clinicians.

7.4.1 Availability and reimbursement of diagnostic tests

The survey results showed that significantly lower frequencies of CTA use were reported by the Swedish respondents compared to the UK respondents. This may be explained by the facts that CTA is increasingly but not widely available in Sweden and that CTA was incorporated into the UK NICE guidelines for patients at low risk of CAD [9,10]. By means of the specific patient cases presented in the survey, MRI was significantly more often reported by UK respondents than by Swedish respondents. Furthermore, respondents from London reported MRI to be more frequently used than respondents from other UK cities. These studies showed a rapid increase in use of cardiac MRI in patients with ACS and striking variations in use between high volume centres, in and around London, and the rest of the country [11]. A major factor that might explain the wide availability and the increased use of MRI scanners in the United Kingdom is the fact that cardiac MRI is funded for assessment of ischaemic heart disease (including suspected ACS) and other heart diseases. The situation is different in many other European countries where different reimbursement schemes are in place and issues regarding reimbursement may need to be solved [12]. Further research would be needed to assess whether the geographical imbalance observed in the responses within and between countries reflects an overuse in the United Kingdom, and especially in London, or underuse patterns outside of London and in other European countries. As cardiac MRI is an accepted modality for assessment of suspected coronary disease, the question of potential overuse mainly relates to the cost-effectiveness of the test.

Although the value of FFR to evaluate intermediate lesions or guide selection of lesions for revascularization in patients with multi-vessel disease is widely accepted [13], modest rates were reported in this survey. This observation might reflect a low use or even a low implementation of FFR in Europe. It might also relate to the fact that the prognostic role of FFR in guiding myocardial revascularization in patients with an ACS needs additional clarification [14,15]. Although FFR-guided PCI has been proven to reduce mortality and MI compared to angiography-guided PCI in patients with stable angina, considerable differences were observed in the survey responses between regions and countries [16]. In that case again, reimbursement remains a major constraint preventing FFR from being

widely utilized in Europe: differences remain between countries that have allowed their hospitals to cover the costs of FFR procedures (like the United Kingdom and Germany) and other European countries where this is not reimbursed [17].

7.4.2 Guidelines

Our findings showed that the reported time between diagnosing an NSTEMI patient and performing invasive coronary angiography varied substantially between and within the geographical areas of the respondents.

Although the European Society of Cardiology (ESC) guidelines recommend revascularization within 24 hours in high-risk patients and within 2 hours in very high-risk patients, this can be a challenge in contemporary cardiac care in Europe [15]. Achieving revascularization within 24 hours was reported as a major challenge for Sweden in the SWEDEHEART Annual report of 2017 [9]. National Institute for Health and Care Excellence (NICE) guidelines recommend coronary angiography within 72 hours for intermediate or higher risk patients [18]. We think that the influence of NICE guidelines in the United Kingdom might partly explain why the times reported by UK respondents show a shift towards later intervention compared to the times reported by the Swedish respondents.

7.4.3 Treatments

The relatively high reported rates of PCI for reperfusion in STEMI patients and for revascularization in NSTEMI patients might reflect a widespread access to PCI throughout Europe. Despite this trend, lower rates of PCI were reported by UK respondents and variations in the answers were seen between all geographical areas; these two observations are consistent with previous studies [19]. European respondents reported PCI as the most common invasive treatment for STEMI and NSTEMI patients, although the efficacy and durability of CABG over PCI (for different groups of patients) was largely demonstrated [20,21]. CABG remains highly recommended in patients characterized by multi-vessel disease, diabetes, or lesion complexity. In Sweden, the volume of CABG procedures has been declining over the past 35 years but considerable differences in the proportion of CABG and PCI out of the total of revascularization exist across hospitals [9]. This large variability might indicate that some patients do not receive the optimal treatment and highlight that further studies would be needed to investigate the optimal rates of CABG and PCI. Comprehensive research is needed on barriers to implementation, and more generally, on factors and structure that determine the diffusion, implementation, and variations in use of PCI within and between European countries.

Finally, we analyzed clinicians' responses regarding whether and when non-culprit lesions are treated and intended to identify possible geographic trends. While guidelines recommend a staged approach in the treatment of patients with STEMI and multi-vessel disease, there is no evidence supporting the superiority of a staged over an immediate approach and no evidence regarding the best approach for NSTEMI patients [13,22].

By means of a survey, this study investigated clinical situations where evidence might remain uncertain or lacking. Indeed, the survey guaranteed that respondents answer to the exact same case, which allows preliminary international comparisons in clinical areas where registry data might not exist, capture limited details, be poor in quality, or not be available to third parties.

7.5 LIMITATIONS

As a main limitation of our study, we acknowledge that a limited number of responses was received, implying a risk of selection bias and constraining generalizability of our results. Further research would be needed to ascertain and generalize our findings. However, our results are consistent with previous studies in the field and identify considerable differences in the reported strategies between areas.

7.6 CONCLUSIONS

Our study revealed considerable variation in the reported modalities of diagnostic and treatment strategies in patients with suspected or established ACS across Europe. We have discussed potential causes for the reported differences in the utilization of these techniques that range from evidence regarding availability of techniques, guidelines, and reimbursement. Such differences may indicate that some patients do not receive the best available care and may have an important impact on the quality of health care and patient outcomes across geographical areas.

Complementary research might be possible to gather generalizable data and confirm these variations, investigate their causes and assess how much they reflect health care inefficiency and result in inequalities in patient outcomes. This could be done by either exploiting existing high-quality registries or setting them up with a specific scope in terms of patient population. The latter might require considerable resources though.

Further research investigating the country-specific cost-effectiveness of diagnostic and treatment strategies in ACS care might be needed to define the most cost-effective way for diagnosing and treating patients per country. Such studies would inform national policy makers and help them decide what cardiovascular technologies to promote and reimburse in order to maximize health gains and/or minimize costs, in the context of their local specificities and constraints. While large European studies such as the SPCCT (Spectral Photon Counting CT) project aim at developing new technologies, stronger evidence regarding current local care, by means of surveys or alternative methods, might be needed before the role and value of new imaging modalities in the clinical arena can be assessed [23].

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SUPPLEMENTAL MATERIAL

SURVEY QUESTIONS

GENERAL QUESTIONS

Q1a: In what COUNTRY is your health centre located?
Q2: In what CITY is your health centre located?
Q3: What is your exact function?
Q4: What is the teaching category of your health centre?
Q5: Is your health centre publicly or privately funded?
Q6: How many myocardial infarction diagnosed patients does your health centre receive annually?

DIAGNOSTIC WORKUP

Q7a: What is the diagnostic workup when a high risk patient is admitted to your health centre with chest pain and an ACS is suspected? Please also precise for what proportion of high risk patients the modality is used?
ECG + biochemical tests
ECG + biochemical tests + non-invasive imaging
ECG + non-invasive imaging (no biochemical test)
Biochemical tests + non-invasive imaging (no ECG)
Other

Q7b: If you marked "other imaging test" in the previous question, please describe the modality used.

Q8a: What is the diagnostic workup when a low to intermediate risk patient is admitted to your health centre with chest pain and an ACS is suspected? Please also precise for what proportion of these patients the modality is used?
ECG + biochemical tests
ECG + biochemical tests + non-invasive imaging
ECG + non-invasive imaging (no biochemical test)
Biochemical tests + non-invasive imaging (no ECG)
Other

Q8b: If you marked "other" in the previous question, please describe the modality used.
Q9b: If you marked "other imaging test(s)" in the previous question, please describe the modality used.

Q9a: What is the usual strategy when a patient over 50 y-o is admitted to your health centre with chest pain and an ACS has been ruled out? Please also precise for what proportion of these patients the modality is used.

Bicycle ECG
Stress echocardiogram
Myocardial scintigraphy
Stress MRI
Invasive coronary angiography
Coronary CT scan
Other

Q9b: If you marked "other" in the previous question, please describe the modality used.

Q10a: About troponin assays as serial testing, please indicate when the first test and subsequent tests (if any) are performed (more than one answer is expected)
In the ambulance
At admission in the hospital
1 hours after symptom onset
2 hours after symptom onset
3 hours after symptom onset
4 hours after symptom onset
5 hours after symptom onset
6 hours after symptom onset
12 hours after symptom onset
Other
Don't know

Q10b: If you marked "other" in the previous question, please describe the modality used.

IMAGING MODALITIES

Q11a: Among all patients presenting with a high probability of ACS after biochemical tests, what are the imaging modalities used to make the treatment decision? For each imaging modality used, please indicate the proportion of the patients that undergo that modality (more than 1 answer is possible).
Echocardiogram
Coronary computed tomography angiography (CCTA)
Invasive coronary angiography with Fractional Flow Reserve (FFR)
Invasive coronary angiography without FFR
Stress echocardiogram
Myocardial perfusion scan
MRI
Positron-emission tomography (PET)
None
Other

Q11b: If you marked ''other'' in the previous question, please describe the modality used.
Q12a: Among all patients presenting a low or intermediate probability of ACS, what are the imaging modalities used to establish the diagnosis? For each imaging modality used, please indicate the proportion of the patients that undergo that modality (more than 1 answer is possible).
Echocardiogram
Coronary computed tomography angiography (CCTA)
Invasive coronary angiography with Fractional Flow Reserve (FFR)
Invasive coronary angiography without FFR
Stress echocardiogram
Myocardial perfusion scan
MRI
Positron-emission tomography (PET)
None
Other

Q12b: If you marked ''other'' in the previous question, please describe the modality used.

Q13a: A 45-year-old female woman suspected with ACS was admitted in the emergency department. She had no cardiovascular risk factor except for smoking during 20 years. She presents with an atypical chest pain, her ECG is normal and her troponin result is low. In this specific case, what further examination(s) would you perform? (more than one answer is possible)
No examination
Invasive coronary angiography
Coronary CTA
Echocardiogram
Stress tests (treadmill/scintigram/stress echo/stress MRI)
MRI
Other

Q13b: If you marked ''other» in the previous questions, please describe the modality used.

Q14a: What proportion of patients presenting with NSTEMI receives invasive coronary angiography? (leave blank if you do not know)

Q14b: What is the average time between diagnosing an NSTEMI patient and performing invasive coronary angiography? (leave blank if you do not know)

TREATMENT

Q15a: Which reperfusion treatment method do you use for patients presenting with a STEMI and no contra indication of treatment? Please also precise the proportion of patients treated with each method.
Percutaneous coronary intervention (PCI)
IV thrombolysis
PVI and IV thrombolysis
Other treatment

Q15b: If you marked "other treatment" in the previous questions, please describe the modality used.

Q16a: Which revascularization treatment method do you use for patients presenting with a primary NSTEMI? Please also precise the proportion of patients treated with each method.
PCI
CABG
Other treatment

Q16b: If you marked "other treatment" in the previous questions, please describe the modality used.
Q17: Following PCI of the culprit lesion, what is THE MOST COMMON STRATEGY for dealing with suspected non-culprit lesions in a 65-year-old NSTEMI patient presenting a relatively good clinical status?
Conservative management and PCI only if symptoms or reversible ischemia on stress test
Elective stress-test (stress Echo/scintigram/threadmill/stress MRI)
Coronary computed tomography angiography (CCTA)
Immediate PCI during index catheterization
Immediate FFR-guided PCI during index catheterization
Staged PCI during index hospitalization
Staged FFR-guided PCI during index hospitalization
Staged elective PCI within 4-6 weeks
Coronary Artery Bypass Graft surgery
Other

FOLLOW-UP IMAGING

Q18a: Do you routinely perform follow-up imaging immediately after interventional therapy and within 4 days after symptom onset? (answers c and d can be combined)
Yes, for all patients
Yes, for STEMI patients only
Yes, for patients presenting clinical deteriorations
Yes, for patients for whom imaging may guide further treatment (surgery or medication)
Never

Q18b: What are the main imaging modalities used as follow-up imaging after revascularization and within 24 hours?

Echocardiogram

Coronary computed tomography angiography (CTA)

Myocardial perfusion scan

MRI

Positron-emission tomography (PET)

Stress echocardiogram

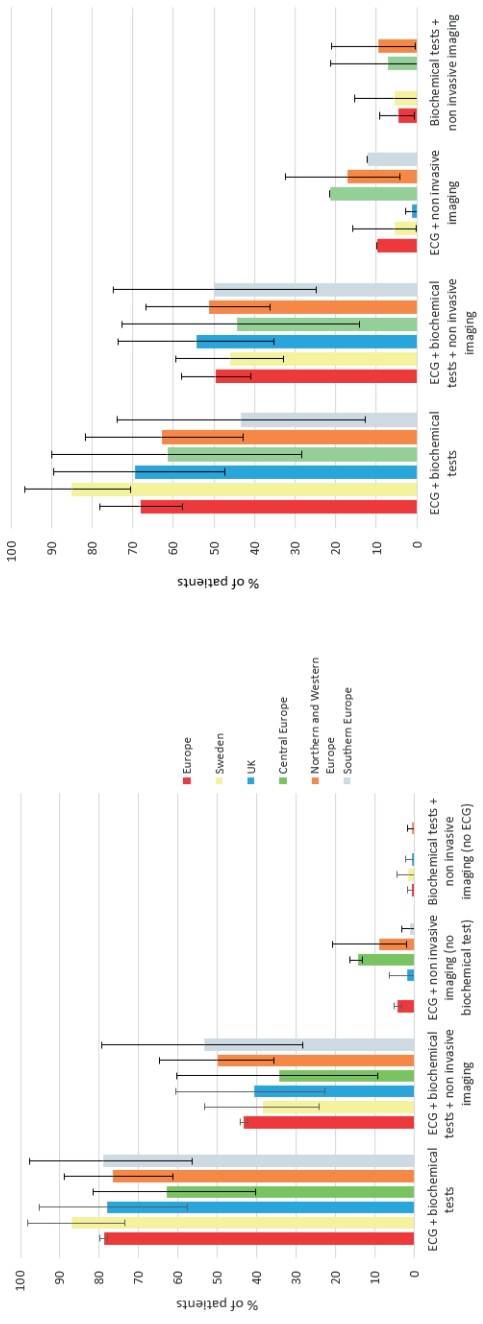
Transcranial doppler

None

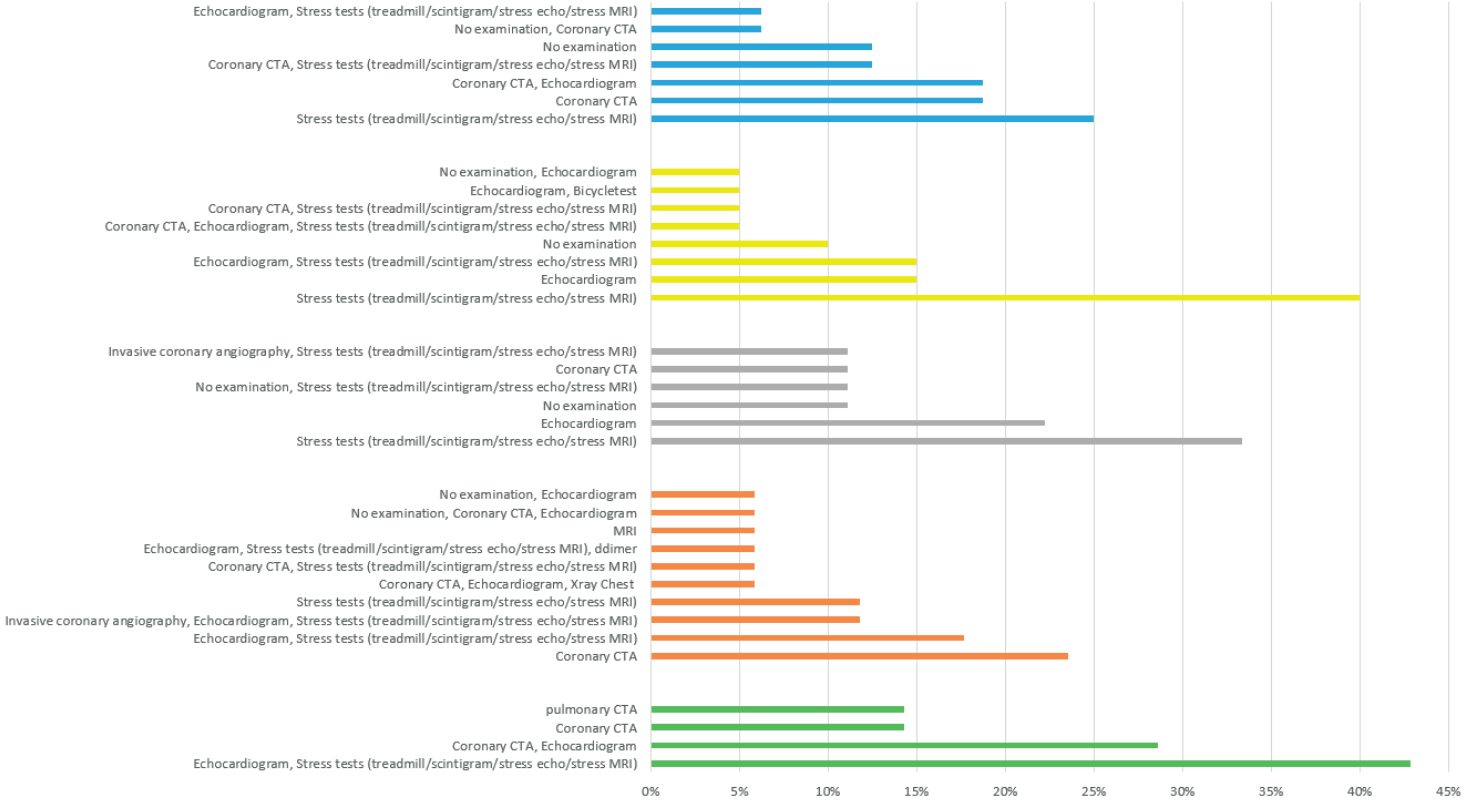
Other imaging test

Q18c: If you marked "other" in the previous question, please describe the modality used.

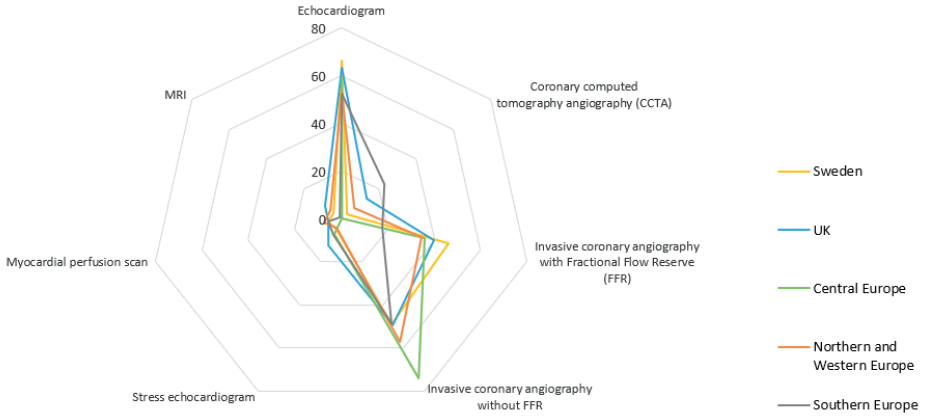
Supplementary figure 1. Reported percentages of patients receiving different diagnostic workups at admission with chest pain and suspicion of ACS.



Supplementary figure 2. Percentages of clinicians reporting to use different examinations in the diagnosis of a low risk patient (patient case 1)



Supplementary figure 3. Reported percentages of patients receiving different imaging modalities when presenting with a high probability of ACS after biochemical tests.
Respondents were asked about the imaging modalities used to make the treatment decision



Timing of troponin assays

Regarding troponin assays used as serial testing, of the 56 respondents who indicated that the first test was performed upon hospital admission, 12 reported no subsequent test, 10 reported a subsequent test at 3 hours after symptom onset and 7 reported a test at both 3 hours and 6 hours. Besides these main trends in serial testing, other respondent reported various combinations of timing, with answers including testing at 2, 4, 5 and 12 hours after symptom onset.

Follow-up imaging after revascularization treatment

In the phase of follow-up imaging used up to 24 hours after revascularization treatment, echocardiogram was reported to be used for an average of 74% of the patients across Europe, far ahead of MRI and myocardial perfusion scan (each modality being reported to be used for 6% of the patients).

8

Cost-effectiveness of imaging strategies to diagnose and select patients with non-obstructive coronary artery disease for statin treatment in the UK UNDER EMBARGO

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Benjamin Clayton, Johan L. Severens

Submitted

9

General discussion

Cardiovascular diseases cause a high humanistic and economic burden worldwide [1-3]. Imaging diagnostic tests have been increasingly used in this field over the past decades, which has transformed the landscape of cardiovascular care but also raised concerns about potential overuse of diagnostics [4,5]. CEAs of diagnostic tests and treatments may inform appropriate clinical use of these techniques while improving medical decision making in a context of limited resources. The aim of this thesis was to assess the potential cost-effectiveness of a currently developed advanced imaging diagnostic technology (SPCCT), for supporting health care decision making in cardiovascular diseases, taking into account international variation. This chapter presents an overview of the main findings of this work, the implications of the results, the challenges encountered, the limitations of our approach and some recommendations for further research.

9.1 MAIN FINDINGS

In a context of variety of imaging and treatment options in stroke care, little was known regarding the diagnostic and treatment workup for patients presenting with a suspected stroke in Europe. Therefore, we conducted a systematic literature review (Chapter 2) and a clinician survey (Chapter 3) to identify the patterns of stroke diagnostic imaging and acute revascularisation treatments in routine clinical practice. We also examined practice variation across European countries. Our systematic review showed that CT was the most widely used imaging modality for diagnosing stroke in Germany, Sweden and the UK. Furthermore, our review highlighted potential variations in the imaging workup of stroke patients, depending on the category of hospital, on timeslots of the day and week and on geographic areas. No evidence regarding the optimal imaging strategy to diagnose stroke patients could be found. Our clinician survey confirmed the pivotal role of CT as the first-line imaging modality to diagnose stroke and revealed CTA as one of the common second-line modalities for ischaemic patients throughout Europe. This information was used to define the comparator (i.e. current care) in our CEAs of advanced imaging. In contrast to these diagnostic-specific findings, considerable variation in the revascularisation treatment for ischaemic strokes was observed across countries, in terms of percentage of eligible patients treated and treatment used (MT or intravenous thrombolysis). Similarly, our second clinician survey (Chapter 7), focusing on clinical practice in ACS, suggested large variations in the diagnostic modalities and acute treatment used across geographical areas in Europe. In both disease areas of stroke and ACS, current care appears to be heterogeneous and little evidence is available to accurately identify and quantify practice variation across countries. Gaining insight into the clinical practice of stroke care and ACS care was necessary to frame the health-economic evaluation of SPCCT.

The potential cost-effectiveness of SPCCT in the diagnostic work-up of ischaemic stroke patients was investigated in different healthcare systems: the UK, the US, Germany, Hungary and Sweden (Chapters 4, 5 and 6, respectively). Our CEAs suggest that advanced imaging (such as SPCCT) to select patients for late MT was cost-effective in the UK (£6,164 to £37,229 per QALY, depending on imaging accuracy and prior probability) and in the US ($662 to $13,877 per QALY, depending on trial data used). A reduced specificity of SPCCT reduced its cost-effectiveness; this effect decreased as the prior probability for patients to benefit from late MT decreased. Moreover, we investigated the cost-effectiveness of SPCCT followed by late MT in 27 subgroups of US ischaemic patients with a large occlusion (i.e. those who are eligible for late MT). Our findings suggest that SPCCT and late MT are cost-effective in all subgroups in the US setting. However, increased uncertainty about the cost-effectiveness was observed for some subgroups (patients with NIHSS[**] ≥16 and patients of 80 years or older). Both our UK-based and US-based models suggest that although it is worth investing in SPCCT, in combination with treatment, more research is needed regarding the (prior) probability that patients will benefit from late MT. Despite the general conclusions regarding the cost-effectiveness of SPCCT in the US and in the UK, we highlighted that the country-specific findings were not generalisable to other countries.

The topic of generalisability of cost-effectiveness models to other settings was addressed in a subsequent step (Chapter 6). More concretely, we combined two frameworks and applied a four-step approach to assess the validity of transferring a decision analytic model from the UK to Germany, Hungary and Sweden. Large variations were observed in the country-specific cost-effectiveness estimates of SPCCT across countries. Although the exact value of SPCCT is country-dependent, this new technology was found to be cost-effective in all investigated countries. Based on our method to assess the process of transferring an original model, we showed different levels of validity of our cost-effectiveness results, mainly related to the quality of the country-specific input data that we used.

Finally, we investigated the potential cost-effectiveness of SPCCT in selecting patients with NOCAD for statin treatment, based on the imaging identification of vulnerable plaques in the UK (Chapter 8). We modelled four different comparators in order to reflect variation in current care and explore the impact of different imaging accuracy levels on the cost-effectiveness of SPCCT. Based on our findings, an improved imaging test with higher sensitivity in identifying vulnerable plaques in patients with NOCAD provides good value for money.

** NIHSS: National Institutes of Health Stroke Scale. Tool used to quantify the impairment caused by a stroke.

9.2 IMPLICATIONS OF OUR RESULTS

The results of our analyses have latent implications at different levels of the healthcare system and for various stakeholders.

Early-cycle health economic evaluations for test developers

Early CEAs and, more generally speaking, early economic evaluations provide key information that manufacturers of the medical industry may use to optimise their product development [6,7]. More precisely, early cycle health economic evidence has been shown to support strategic research and development decisions (including portfolio management), preliminary market assessment and preliminary pricing and reimbursement estimates [8]. The contribution of our early-HTA work to manufacturers is mainly valuable in guiding the research development phase of SPCCT and in providing some preliminary estimates of the market potentials in two disease areas. First, in the initial phase of the SPCCT project, expert panels were conducted that engaged radiologists, neurologists, cardiologists, physicists and health economists from academia and the industry, both internal and external to the project, in early dialogues. These "scoping" meetings gave birth to a preliminary inventory of the potential uses of an improved photon-counting imaging test in clinical practice. The most promising use of that inventory was ascertained through a process of external and independent validation with clinicians in different countries. As such, we elicited the most likely use of SPCCT in terms of disease area (acute ischaemic stroke and NOCAD), the potential sequence (single replacement test) and application (diagnostic, prognostic and/or companion diagnostic test to decide on a therapy). These elicitations were also refined according to the results of our systematic literature reviews and clinician surveys (Chapters 2, 3 and 7). In that respect, it is interesting to note that the findings described in Chapter 7 (survey of current care in ACS) led to a shift in the potential use of SPCCT in cardiac care, namely from ACS to NOCAD area. Second, we investigated the impact of the diagnostic performance (sensitivity and specificity) of SPCCT on the cost-effectiveness results (Chapter 4 and 8). Our results showed that specificity should be favoured over sensitivity in the diagnosis of stroke patients, while sensitivity should take priority in the diagnosis of NOCAD patients. These findings are concrete elements that should determine the technical features and specifications related to the performance of SPCCT. With this information at hand, manufacturers are better equipped to anticipate and mitigate the risk of developing a new complex technology and can thereby maximise their return on investment. In Chapter 4, we also investigated the impact of the prior probability to benefit from late MT on the cost-effectiveness of SPCCT. By doing so, we also provided preliminary indications of the market potential for SPCCT in stroke care. We highlighted the multi-level uncertainty around our cost-effectiveness estimates: parameter uncertainty,

structural uncertainty but also heterogeneity caused by patients' characteristics. Given this uncertainty, the complexity and high cost of advanced imaging test development, a dynamic and iterative process of integration of the newest evidence and adjustment of the product specificities is recommended [7]. This iterative process should also capture other important stakeholders' perspectives, among which the clinician's perspective is essential.

Clinicians

As previously mentioned, internal and external clinicians are continuously involved along the development phase of a medical product. They provide feedback and advise on the indications and applications that a new technology could have in clinical practice. In addition, clinicians may influence the trade-off level between sensitivity and specificity of a new diagnostic test. As such, clinicians make an explicit bridge between the industrial and clinical worlds, which is essential to guarantee the applicability and relevance of industrial products in the healthcare setting. Their contribution in all phases of our early-HTA work (framing, structuring, making assumptions, analysing the results) was also essential to articulate the medical and health economic concepts and ensure the clinical validity and relevance of our models. In the absence of RCTs, results of early decision-analytic models provide preliminary evidence for medical decision making that needs to be ascertained by clinicians. In addition to this continuous consultancy role to the manufacturer and health economists, clinicians are key opinion leaders at the hospital level who play a substantial role during the selection and implementation process of a new diagnostic test. The acquisition of a diagnostic imaging device is a large and potentially risky financial investment in an equipment expected to have a long economic life in the hospital. Therefore, it is essential that clinicians understand how a new medical product addresses concrete clinical needs, in terms of both health outcomes and process outcomes. Furthermore, the implementation of a new imaging diagnostic tool might have extensive implications in the organisation of care at local and regional levels. If the choice was made to implement stroke advanced imaging in only a few hospitals countrywide, these hospitals would certainly become regional hubs for the diagnosis and triage of suspected stroke patients. This would have consequences in terms of the human and material resources needed in these hospitals to absorb the incoming flow of patients from a vast region. On a more practical note, it is important to keep in mind that clinicians are the end users of diagnostic devices in their daily work. Reluctance to change and bias towards more traditional, gold standard or expert-driven modalities might play an important role in the way clinicians and opinion leaders influence the introduction of new diagnostics into clinical practice or even into clinical guidelines [9].

Policy makers and national payers: reimbursement, clinical guidelines and future research

The assessment of diagnostics in Europe is untransparent and often relies on a reimbursement review at the local or regional level, which contrasts with the national process generally applied to drug reimbursement decisions [10]. In addition, diagnostic tests are often reimbursed through a DRG payment in Europe. In this context and given the early HTA nature of our analyses, it is unlikely that our work can directly be used to inform reimbursement decisions by the payer (i.e. government or insurer). However, our analyses clearly showed that advanced imaging, used to inform MT treatment, provides high value for money across the different investigated countries (UK, US, Germany, Hungary and Sweden) (Chapter 4, 5 and 6). In a universe where cancer drugs and drugs for rare genetic illnesses are being paid for at millions of dollars or euros per QALY gained, the ICERs that we presented in our results imply that major public investments should be made in MT, and therefore, in prerequisite diagnostics to this treatment. Given the magnitude of the effects of MT and the likelihood that interventions improving functional outcomes in stroke are highly cost-effective, our results might influence future positive reimbursement decisions. Most importantly, our results provide an understanding of the science that relates to particular clinical decisions and might encourage healthcare authorities to revise clinical guidelines both in the field of stroke (time of treatment since onset, explicit imaging criteria required for treatment) and NOCAD (systematic imaging-based decision to select patients for statin therapy). Our work might also stimulate healthcare authorities to commission additional research that will be needed to achieve future reimbursement decisions. Major parameters driving decision uncertainty were identified (e.g., prior probability to benefit from MT, long-term post-stroke costs, test accuracy), which might serve as a basis to set the research agenda, preferably based on explicit value of information analyses. Future policy questions might address the magnitude of the cost-effectiveness across heterogeneous subgroups or the maximum number of endovascular treatments that the annual budget can bear, for example.

Early health economic evaluations for research and beyond, gaining international insight

Our model-based analyses in the area of stroke essentially confirm the existing health-economic knowledge regarding the value of MT while pushing the boundaries of evidence further, with an emphasis on the impact of advanced imaging and patient heterogeneity on the ICER (Chapters 4 and 5). Our model-based analysis in the field of NOCAD presents new evidence regarding the potential value of an improved test on plaque assessment for selection of patients for statin treatment (Chapter 8). Given the fact that no model is perfect, there is a necessity to compare the results of different models investigating similar research questions and scrutinise their methodology in the

quest for convergence validity. In that respect, our work contributes to the scientific understanding of the link between disease progression, disease-related cost structure and the positioning, requirements and usefulness of a new imaging technology in stroke and NOCAD care. Based on evidence synthesis, our early-HTA work converted raw numbers into results and information that are relevant to the scientific community. Finally, in spite of the heterogeneity in the role of HTA across European countries, our country comparison (Chapter 6) demonstrated, through a unique methodology (early cost-effectiveness), that the exact value of SPCCT is country-dependent. Although SPCCT has a country-specific value, it appeared to be uniformly cost-effective across the countries that we investigated. In that respect, our country comparison provides valuable international insights and may contribute to lowering barriers to market access for advanced imaging in countries that have a slower rate of adoption of new technologies, such as Hungary. Based on recent evidence, countries that are ''recent'' adopters of HTA (such as Hungary and, more generally, Central and Eastern Europe) consider the decision made in ''early HTA adopter'' countries (such as England, Germany, Sweden, or France) to inform their own final decision regarding the reimbursement of drugs [11]. Anchoring a Hungarian decision on the use of the appraisal decision of another European country might not reflect the local conditions, priorities and values. Our analysis (Chapter 6) highlights the need to use local data as input for final decision making while providing strong preliminary evidence of the value of SPCCT in Hungary.

9.3 CHALLENGES ENCOUNTERED

Assessing current care

Three chapters of this thesis were dedicated to the assessment of current care in routine clinical practice (Chapters 2 and 3 related to stroke care, and Chapter 7 related to ACS care). In this attempt to gain insight into current care, we faced major challenges caused by the lack or unavailability of data. On the one hand, literature reviews tend to be generated late which introduces a time mismatch between the availability of evidence and the moment data are needed to perform HTA analysis. On the other hand, while surveys offer the advantage of their flexibility and specificity to a topic of interest, their results may not be representative or generalisable. Finally, registries are often exclusive to rare diseases or cancer care and present various limitations. In this context, and due to the international scope of our analyses, the assessment of current care turned out to be challenging, which was addressed via complementary methodologies (reviews and surveys).

Choosing a unique comparator in a context of healthcare variation

Given the incremental concept that forms the backbone of the methodology in CEAs, the choice of a relevant comparator was essential to determine the value of the health technology being assessed. Given the substantial practice variation across countries in terms of diagnostic imaging techniques used in stroke care, the choice of a comparator was challenging. Based on the results of our European clinician survey, CT + CTA was identified as a general, widespread and most likely comparator to be used in our European-based CEAs (Chapters 4 and 6). In contrast, in Chapter 5, our comparator was chosen based on the imaging modalities used in the DAWN and DEFUSE 3 trials (CT+ CTA or MRA + CTP or MRI). Large practice variation in diagnostic techniques used in the field of stroke care exists, which suggests that the value of SPCCT should be assessed against that of multiple comparators (including relevant combinations of imaging tests) or against a realistic mix of diagnostic technologies. We could have adjusted the structure of our stroke model (Chapter 4 and 6) and included more comparison arms to reflect variation in current care, which would have reduced the structural uncertainty. However, for feasibility reasons, for the sake of obtaining findings that are useful at healthcare system level and in line with clinicians' inputs, we simplified our research to a single comparator (stroke analyses). Given the lack of evidence regarding the standard assessment and selection of NOCAD patients for statin therapy, we decided to model more comparison arms in the related model (Chapter 8). In the case of large practice variation, hospital-level CEAs might be particularly relevant as part of the evidence needed to inform decisions made at hospital level (such as buying a new imaging device).

Early HTA: modelling the unknown and dealing with uncertainty

Given the early phase of development of SPCCT, the most likely clinical indications where this new imaging technology could add value was uncertain. Scoping meetings with clinicians highlighted different viewpoints and a lack of consensus regarding the potential use (diagnostic, prognostic, screening, follow-up) of SPCCT and the patient populations most likely to benefit from this new technology. Specifically, while the diagnosis of ACS initially appeared to be a prospective area where SPCCT could add value, a final decision was made to center our CEA on NOCAD. Furthermore, for feasibility reasons, we limited the value assessment of SPCCT to two disease areas (ischaemic stroke and NOCAD) while in reality, SPCCT could have increased value in various other indications, and even in other disease areas. Most importantly, once implemented in clinical practice, SPCCT will not be limited to one indication but will rather serve a range of diseases, clinical applications and patient populations, which will influence its average cost-effectiveness. Furthermore, at the time of our analyses, the accuracy of SPCCT per medical condition was unknown, which was addressed by different methodologies. Concretely, different pairs of sensitivity and specificity were simulated in a scenario-

based analysis in Chapter 4, a perfect test was modelled in Chapter 6 and two SPCCT-based strategies were modelled in Chapter 8. Finally, a substantial part of our work was dedicated to measuring uncertainty around our results. The uncertainty around the current care estimates (Chapters 3 and 7) was explored by means of the non-stochastic simulation method of bootstrapping. Multivariate parameter uncertainty was addressed by means of stochastic simulations in PSAs (Chapters 4, 5, 6 and 8). In addition to the CEAC(s) presented in these four chapters, confidence intervals around the deterministic results and deterministic 1-way sensitivity analyses were introduced in Chapter 5. These various methods were chosen to address the dual challenge of dealing with and efficiently communicating uncertainty to different stakeholders. Although we primarily focused on the impact of parameter values, structural uncertainty, resulting from the model design and the various structural assumptions, is probably a major source of uncertainty worthy of further investigation [12]. While our modelling work in the field of stroke care benefitted from relatively mature research, with available models and data, modelling NOCAD involved greater structural uncertainty, mostly driven by the lack of robust evidence regarding current care and treatment efficacy. Future research will be needed to more specifically address the joint structural and non-structural uncertainty, especially in the field of NOCAD. ''Disease-specific model standardisation'' might be an approach to decrease structural uncertainty [12,13].

Simplifying reality

A model is a simplification, and therefore an approximation, of reality, based on framing, assumptions and the input data (e.g., cost data, disease progression, quality of life data). There is a tradeoff between accuracy (adequation between the model and the reality) and feasibility, which, as such, presented a first challenge. In the phase of structuring the model, it can be difficult to assess which level of precision and complexity is needed to obtain accurate results without making the data collection exercise impossible. Another major structural simplification lay in the fact that we modelled the crude discrete probabilities to benefit from late MT (stroke care, Chapter 4) (probabilities of 10%, 20% and 30%). Ideally, we would have modelled the explicit clinical imaging markers (volume of infarcted tissue, volume of salvageable brain tissue or penumbra, for example) used to predict patients' outcome and referral to treatments [14-16]. Given the lack of evidence regarding these concepts, in terms of imaging thresholds or prevalence, these physiological findings were not explicitly modelled. In addition, a second challenge inherent to any modelling exercise related to the limited data available. Specifically, in our work, cost data for SPCCT were not available and were based on assumptions. In addition, the paucity of available and existing stroke data in Germany and Hungary, respectively, hampered the accuracy and the validity of these countries' estimates (Chapter 6). While the state of evidence related to the disease progression and treatment efficacy in stroke care

is relatively mature, we encountered an extreme paucity of data in the area of NOCAD and our modelling work had to rely on numerous assumptions (Chapter 8). Finally, we presented deterministic results that essentially are costs per average patient, which is a concept that does not exist in the real world. On the contrary, between-patient variation might be substantial and the impact of this variation on the ICER could be addressed by means of alternative research methods (such as discrete event simulations).

Assessing diagnostics

Given the indirect and uncertain effects of a test on patient's outcomes (via treatment), the value appraisal of diagnostics is more complex than that of drugs and requires extensive knowledge of the post-diagnosis care pathways [17]. Due to this indirect effect, it can be challenging to disentangle the value of an imaging test from the value of the treatment or procedure delivered based on the test's results. The value assessment can be even more challenging when, in combination to the treatment, the patient modifies his lifestyle (smoking or exercise, for example) based on the information provided by the test, which would typically be the case for NOCAD patients selected for statin therapy. Furthermore, the benefit of a correct diagnosis, the potential harm of a false-positive diagnosis and the loss of benefit in a false-negative case, in the short- or long-term, are strong drivers of the value of diagnostic tests that go beyond the technical performance (sensitivity and specificity) [18]. The value of a diagnostic test also depends on the pre-test probability of the disease or condition, which may not be precisely known [18]. In case additional tests are used in clinical practice, they will change the prior probability before the subsequent test, which will impact the value of the diagnostic technology being assessed. Finally, there may be adverse effects of performing the test, caused by the toxicity of the contrast agent used or the exposure to radiation [18]. The clinical and economic value of diagnostics is therefore the result of many variables that all need to be taken into consideration during the value assessment.

9.4 LIMITATIONS OF OUR APPROACH

We acknowledge different methodological limitations in our work.

Narrow classical approach: CEA

Besides the limitations of the individual studies described in the Chapters, the main limitations of our work come from the narrow classical approach to determining the value of a health technology for the purpose of its reimbursement at healthcare system level. With this approach, we fail to capture the comprehensive value that SPCCT might offer to various stakeholders in the healthcare and societal arenas. The results that we

provided (ICER) represent the general healthcare cost per QALY gained per patient. At hospital level, these results might be heavily impacted by local factors, ranging from the volume of patients scanned per year, the patient case-mix (in terms of age, disease or comorbidities) and the human and material capacity to deliver acute treatments following diagnosis. We touched upon the impact that the cost of RAPID software (needed in addition to CTP or MRI, to inform treatment decisions beyond 6 hours from stroke onset) might have on the cost-effectiveness of advanced imaging at hospital level (Chapter 5). The annual cost of the software per hospital varies substantially per institution ($17,500 to $52,000 in the US), depending on the use and configuration (for one scanner or unlimited software license). Considering that the annual software cost would be divided among the annual number of patients scanned, the cost-effectiveness of advanced imaging might considerably vary across hospitals. In addition to the software costs, critical capital equipment investment is involved when it comes to acquiring imaging diagnostics. Cost-effectiveness evidence at hospital-level is needed to inform hospital managers regarding their investment decisions. Furthermore, hospital-specific cost-effectiveness estimates might be needed to optimise the organisation of stroke care, based on the number and localisation of diagnostic- and/or treatment-capable hospitals at country level. While reimbursement of the patient scans is a key criterion for investment, budget considerations are also essential in the strategic investment choices that hospital managers are responsible for. As such, the approach used to inform decisions applicable at a healthcare system level may not be suitable for decisions applicable at a healthcare provider level where complementary decision tools might be needed.

Relevance of hospital-based HTA or mini-HTA

Compared to CEA, mini-HTA provides a broader HTA approach to decision making. Mini-HTA is a comprehensive management and decision support tool targeted at hospital managers and clinicians which aims at a strong role for healthcare providers [19,20]. The tool is intended to promote informed decision making regarding the acquisition (i.e. purchase) of a new health technology, taking into consideration scientific evidence (for patient benefit) combined to the impact on the hospital in the context of its organisation, culture and economic considerations [19, 20]. The dimension of value at hospital level may be captured through safety, patient impact and benefit, cost-effectiveness, quality of evidence and level of innovation [21]. The dimension of risk may be broken down into the impact on staff and space, incremental and net costs and the investment effort required [21]. Most of these variables were not incorporated in our cost-effectiveness-based value appraisal. Various initiatives of mini-HTA or hospital-based HTA have been developed in recent years [22]. Although their approaches seem unharmonised, these initiatives reflect a clear general need for hospital-based evidence when medical technologies, and particularly imaging diagnostics, are to be acquired. Among the recent

approaches, a tool combining mini-HTA and multi-criteria decision analysis (MCDA) was developed, also reflecting the growing need to incorporate the opinion of end-users (i.e. clinicians) into the hospital decision making process [23].

Beyond CEAs: MCDA and budget impact

We touched upon some of the limitations of the cost-effectiveness framework with regards to its general implications at healthcare system level. Fortunately, HTA is a much more comprehensive discipline which offers complementary methods addressing other important concepts than value, such as equity or affordability.

MCDA is a potential contributor to decision making that involves a broader and flexible set of criteria or benefits, compared to the restricted cost per QALY gained (captured by the ICER). MCDA allows for a systematic, explicit, transparent trade-off between various relevant criteria in the decision-making process [24]. This method offers the advantage to account for multiple stakeholders' perspectives [24]. The included criteria vary widely and include disease prevalence, disease severity, life expectancy of a patient left untreated, effectiveness of intervention and whether the condition is related to patient risk behavior. Noteworthy is the fact that the ICER can be part of the MCDA. In line with this approach, a recent comprehensive benefit-risk framework specifically assessing the value of imaging diagnostics identified 36 criteria classified into three domains: test or device attributes, clinical management or provider experience and patient experience (Table 9.1) [25]. These criteria are subject to trade-offs across diseases and patients' or providers' preferences. Furthermore, the choice of criteria depends on the disease or indication. While the missed cases, the examination time or the patient preparation requirements might be essential criteria in acute stroke care where ''time is brain'', criteria related to patient experience (radiation, toxicity of contrast agent) may be more relevant in the area of NOCAD.

Table 9.1 Benefit-risk criteria for the assessment of diagnostic imaging, categorised into 3 domains [25]

Test-specific Features	Patient Management and Provider experience	Patient experience
Missed cases	Therapeutic/procedural success	Value of knowing
False diagnoses	Potential for additional confirmatory testing (inconclusive/false-positive results)	Disvalue of knowing
Diagnostic accuracy consistency	Potential for incidental finding management	Burden (time and money) to patient
Interobserver reading agreement	Net unnecessary treatment (test prescribed or averted treatment)	Patient comfort
Depth/breadth of anatomy visualisation	Access to test	Patient future compliance and behaviour
Invasiveness/risk of adverse events	Time to diagnosis	Radiation-induced cancers
Contrast reaction potential	Inpatient/outpatient healthcare visits	Length/quality of life
Ionising radiation dose	Time to discharge	
Patient-specific exclusions	Provider utility	
Failure/malfunction rate	Liability protections	
Patient preparation requirements	Financial incentives	
Examination time	Contribution of information to prognosis	
Post-test observation time		
Decision support		
Portability		
Ease of use		
Reimbursement potential		

Finally, while we have clearly showed that advanced imaging for referral to MT provides high value (in terms of cost per health outcome), we have not assessed the affordability of the intervention (diagnosis + treatment) at country level. Affordability can be evaluated by means of a budget impact analysis which is generally conducted in addition to the "companion" CEA [26]. A budget impact analysis accounts for the number of patients who need the intervention (stroke incidence for instance) multiplied by the cost of the intervention at a short time-horizon (a few years). This analysis allows national payers to quantify how using the technology in clinical practice will affect their budget and is often used for resource planning and budget allocation. Affordability is a key element determining patient access to treatment. In the case of stroke, in spite of the high value of advanced imaging and MT, it is likely that some governments cannot afford to cover the costs of diagnostic and treatment for all clinically eligible patients. An intervention might be highly cost-effective but unaffordable at population level, which suggests that priority should be given to certain patients according to country-specific prefer-

ences (younger patients, patients with the greatest needs or patients most likely to benefit from treatment, for example). Finally, a budget impact analysis, incorporated as an element of mini-HTA, could be highly relevant to decision makers. Budget impact analyses performed at hospital level might support the idea that high-cost diagnostic technologies should be concentrated in a few specific hospitals or clinics rather than widely spread.

One method does not fit all countries

We provided international insight into the value of SPCCT in the UK (Chapter 4 and 8), in the US (Chapter 5) and in Germany, Hungary and Sweden (Chapter 6). Our country-specific results are based on the single methodology of cost-effectiveness, which might not equally be suited to the different investigated countries. While the UK, Germany and Sweden strive for a better quality and equal access to care combined with an efficient use of resources, Hungary places increased attention on budget considerations during the pricing and reimbursement decision-making process [11]. In contrast, the US has historically been less inclined to financial constraints in healthcare [27]. Germany follows the principle of added therapeutic benefit and requires health economic evidence (cost-benefit analyses) for reimbursement decisions only when no agreement on the reimbursed price is reached [11]. These different uses of HTA across European countries show that country-specific methods should be used to assess the country-specific value of healthcare technologies, especially if the value appraisal is intended for reimbursement.

To a certain extent, and in the interest of patients across countries, our work questions the necessity of a more harmonised international HTA system to ensure timely and equitable access to new high value healthcare technologies. EUnetHTA (European network for HTA) has the mission ''to support collaboration between European HTA organisations that brings added value to healthcare systems at the European, national, and regional level" [28]. Despite the EUnetHTA achievements, concern has been raised regarding the untransparent and heterogeneous reimbursement decisions across countries for a similar drug-indication [29]. To date, despite growing efforts focused on the assessment of medical devices by EUnetHTA and other HTA organisations, no evidence regarding the appraisal process for expensive imaging diagnostics is available. The challenges and specificities related to the reimbursement of diagnostics suggest rather more heterogeneity than less, compared to pharmaceuticals.

9.5 RECOMMENDATIONS FOR FUTURE RESEARCH

We have provided an early insight into the potential value of SPCCT. Further research is needed to confirm our cost-effectiveness estimates. First, real world data are needed to understand what imaging modalities are currently used in clinical practice for the diagnosis of stroke and NOCAD patients at hospital level, national level and international level. Real world data based on registries, patient electronic dossiers or big healthcare data might be ways to obtain high quality data, especially in countries characterised by less research capacities. Value of information analyses using our models could be helpful to set the research agenda and priorities regarding data collection. Second, clinical studies of SPCCT (trials and observational studies) should be conducted to provide solid evidence regarding the clinical efficacy. The potential harms of testing should also be investigated. More generally speaking, the value assessment of SPCCT from a patient perspective might be relevant. Third, structural uncertainty related to the framing of our CEAs should receive additional attention. This particularly needs to be addressed in the area of NOCAD, where more robust evidence regarding long-term statin efficacy is necessary. Disease-specific standards for modelling might contribute to a higher quality of the health-economic evidence. Fourth, further research should investigate the optimal deployment of advanced imaging diagnostic based on the organisation of acute stroke care at country level. Since the value of advanced imaging operates via treatment, it is necessary to optimise the network of care according to the country-specific practical constraints, in terms of budget, manpower, geography, infrastructures and culture. Fifth, there is a limit to the price of advanced imaging per patient beyond which the country-specific conventional cost-effectiveness threshold, if any, will not be met. Headroom analyses should be conducted to determine the maximum price of an advanced imaging scan per stroke patient and NOCAD patient according to the national willingness-to-pay threshold. Headroom analyses could also inform value-based pricing and should be conducted for each indication of SPCCT. Finally, international harmonisation of the HTA process for reimbursement might be needed to promote fairness and equitable access to care for patients across countries. The relevance and mandate of international organisations such as EUnetHTA to promote HTA harmonisation throughout European countries in favour of equal access to care should be determined.

GENERAL CONCLUSION

Despite a lack of data and considerable practice variation across countries, we have used modelling techniques to assess the cost-effectiveness of complex diagnostic strategies in cardiovascular diseases. More specifically, we estimated the country-specific cost-

effectiveness of the currently developed SPCCT modality in stroke and NOCAD care and identified the technical drivers of the value per disease area. We explained the relevance of our early HTA findings to the manufacturer and highlighted the necessity to sharpen our cost-effectiveness estimates once more evidence and (quality) data become available. The evidence of value of SPCCT might be required by decision makers or payers at a later time. Although CEAs form a solid pillar in value assessment regardless of the level of decision making, they present limitations that complementary methods incorporating different stakeholder perspectives may overcome. Depending on the stage of diffusion and implementation of SPCCT, later in its life cycle, a more comprehensive approach including mini-HTA, MCDA and budget impact analyses might become relevant. In the current phase, our economic analyses present strong and useful evidence of how SPCCT is expected to be a promising diagnostic technology in cardiovascular diseases.

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SUMMARY

Worldwide, in a context of diffusion of medical technologies and increasing healthcare costs, there in a strong need for scientific evidence to support the decision-making process regarding the use and financing of new technologies. Health technology assessment (HTA) is the systematic evaluation of the direct and intended effects of a health technology, as well as its indirect and unintended consequences. Economic evaluations are the core of HTA and provide insight into the costs and effects of a new technology compared with another one, which, in many occasions, is current care. The methods of cost-effectiveness analysis and cost-utility analysis are commonly used, leading to the generic efficiency outcome of cost per quality-adjusted life year (QALY). Framing is a crucial initial step of a cost-effectiveness/utility analysis, which includes defining the patient population, the intervention, the comparator, and the perspective. Framing also is required when evidence from various sources is mathematically synthesised in a decision analytic model. The key purpose of decision modelling in healthcare is to provide evidence for decision-making under the conditions of uncertainty. Decision model uncertainty is threefold: it includes the uncertainty related to the values of the parameters used, to patient heterogeneity and to the structural choices that are behind the model, such as the clinical events and statistical methods used. Making these concepts of uncertainty explicit, early HTA can also be used alongside the research and development phase of a new technology to inform the manufacturer and other relevant stakeholders about the potential value of the technology. This is especially relevant for diagnostic technologies since early decision analytic modelling may encourage developers to adjust the technical features to improve the value of new diagnostics for treatment decisions, patients, healthcare providers, manufacturers, and more generally, society. A positive value assessment might lead to favourable decisions regarding purchase and/or reimbursement by healthcare providers and healthcare authorities. Finally, since the value of a health technology is highly dependent on the healthcare system context, transferring health economic evidence from one country to another might be a fast and efficient method to inform decision makers in various jurisdictions.

Diseases

Leading cause of death and associated with a high humanistic and economic burden globally, cardiovascular diseases (CVD) are a group of disorders of the heart and blood vessels, that include coronary heart diseases and cerebrovascular diseases. The large majority of CVD cases is caused by atherosclerosis, which is the deposit of fatty materials (or plaques) on the inner wall of arteries. Plaques and plaque rupture or erosion can cause vessel occlusion and lead to cardiovascular events, such as acute coronary syndrome (ACS) (including myocardial infarction (MI)), stroke and/or death. The new

emerging and innovative imaging technology spectral photon-counting computed tomography (SPCCT) could potentially add value in the diagnostic workup of patients experiencing or being at risk of a cardiovascular event.

This thesis focuses on two major cardiovascular disorders: ischaemic stroke and coronary artery disease (CAD), with ACS and non-obstructive coronary artery disease (NOCAD). First, acute patients presenting with stroke-like symptoms need to receive a timely assessment of the cause and nature of brain damage before clinicians can decide on the type of acute treatment. SPCCT is expected to improve acute stroke treatment decision-making by a better quantification of brain perfusion impairment. Second, patients presenting with chest pain or discomfort require an assessment of the cause of their complaints before treatment can be determined. By its higher sensitivity to calcification and increased spatial resolution, SPCCT is expected to improve the accuracy of coronary stenosis measurement and the characterisation of atherosclerotic plaques in terms of their structure and biology. With this level of information, SPCCT is expected to identify plaques that are at risk of rupture and to guide the decision of preventive treatment in CAD.

This thesis

The overall objective of this thesis is to assess the potential cost-effectiveness of the currently developed advanced diagnostic imaging technology SPCCT, to support healthcare decision-making, taking international variation into account. Four main research questions are covered. First, what is known about current care and its variation in four European countries regarding the diagnostic workup and therapeutic interventions for patients presenting with a suspected stroke and patients presenting with ACS? Second, what is the cost-effectiveness of SPCCT in ischaemic stroke patients in the United Kingdom (UK) and the United States of America (USA)? Third, is there international variation in the cost-effectiveness of SPCCT for patients with ischaemic stroke and is the transfer of an economic model a valid method to obtain country-specific estimates? Fourth, what is the cost-effectiveness of SPCCT in patients with NOCAD in the UK?

The studies

In **Chapter 2**, a description of the currently used stroke imaging technologies and practice variation across Germany, Hungary, Sweden and the UK is provided. This information is needed to reflect current clinical practice in our subsequent cost-effectiveness analyses. In a systematic literature review, original studies reporting the imaging workup used in acute stroke care were identified. Following the design of a de novo search strategy, five databases were consulted, and fifteen studies were included in the final analysis. Most of the selected articles were observational studies based on national registries.

No study was identified for Hungary. Computed tomography (CT) was reported as the main diagnostic imaging modality used in stroke care. Evidence regarding the optimal imaging approach to diagnose stroke patients is lacking. Furthermore, evidence was insufficient to make an accurate between-country comparison of the imaging workup used in stroke care.

A variety of imaging and treatment options for stroke treatment exists. In order to complement the findings of Chapter 2 and examine current practice, we developed a web-based survey that was distributed to clinicians throughout Europe. Despite a low response rate, we presented responses from Sweden (21), the UK (16), Hungary (15), Germany (12) and Europe (47) in **Chapter 3**. Variation in acute stroke diagnosis across European countries appeared to be limited regarding the first-line imaging test (CT used for 81% to 93% of patients). However, variation increases at later stages of the imaging workup and in the choice of treatment. German and UK respondents reported that 81% and 12%, respectively, of their patients with a large vessel occlusion diagnosed within 4.5 hours received intravenous thrombolysis and thrombectomy. For patients diagnosed with an extensive ischaemic stroke within 2 hours from onset, 75% of the UK-respondents stated thrombectomy as their preferred revascularisation treatment, but only 13% reported to use it. We conclude that further research is needed to compare the quality of stroke care across countries and determine the most cost-effective second-line imaging workup to diagnose stroke patients.

In **Chapter 4**, we compared the cost-effectiveness of two care pathways for acute ischaemic stroke patients in the UK: mechanical thrombectomy (MT) limited to 6 hours after symptom onset based on conventional imaging versus MT within and beyond 6 hours based on selection by advanced imaging. For this purpose, we developed a decision tree (representing the short-term diagnostic and treatment phase) and a Markov trace (representing the long-term post-stroke evolution until death) and modelled the progression of a hypothetical UK-cohort of patients aged 71. Various scenarios based on different values of prior probability to benefit from late thrombectomy and imaging accuracy were evaluated. In addition, probabilistic sensitivity analyses were conducted. Incremental cost-effectiveness ratios varied from $8,199 (£6,164) to $49,515 (£37,229) per QALY gained. Our analyses showed that advanced imaging accuracy impacted the incremental cost-effectiveness ratio mainly when its specificity decreased. Over a lifetime horizon, all scenarios including late MT improved QALYs. Depending on the scenario, the probabilistic sensitivity analyses showed probabilities varying between 46% and 93% for the late MT pathway to be cost-effective at a willingness to pay threshold of $39,900 (£30,000) per QALY. We show that, in principle, late MT up to 12 hours from symptom onset may be good value for money. However, additional data are needed

regarding the implementation of advanced imaging and prior probability for patients with an ischaemic stroke to benefit from late MT before the cost-effectiveness can be fully assessed.

Recent evidence (DAWN and DEFUSE 3 trials) regarding the functional benefit of late MT at a 3-month follow-up showed that MT might be beneficial up to 24 hours from stroke onset. Delivering MT in the late treatment window (between 6 and 24 hours from symptom onset) requires advanced neuroimaging selection of patients. In **Chapter 5,** we presented whether the short-term functional benefit of late MT based on advanced imaging and standard medical care (SMC) translates into cost-effectiveness in the USA over a lifetime, compared to SMC only. Adopting a US healthcare perspective, a cost-effectiveness model combining a decision tree and Markov trace was designed and populated with the results of the DAWN and DEFUSE 3 trials. For the total trial populations, the ICERs were $662/QALY and $13,877/QALY, respectively. Late MT+SMC (versus SMC only) has a 99.9% probability of being cost-effective at the willingness to pay of $100,000/QALY. Subgroup analyses revealed a wide range of probabilities for MT+SMC to be cost-effective at $50,000/QALY, with the greatest uncertainty observed for patients with NIHSS≥16 (National Institutes of Health Stroke Scale) and patients of 80 years or older.

Chapter 6 presented the international variation in the value of SPCCT for ischaemic stroke patients and a methodology to assess the validity of transferring cost-effectiveness evidence from a country to another. A 4-step approach combining the framework by McCabe and Welte was developed and implemented to assess the validity of transferring the decision analytic model of Chapter 4 from the UK to Germany, Hungary and Sweden. The UK model appeared to be relevant for the 3 decision countries. Transferability limiting factors were identified which led to the localisation of input data per decision country. A step was dedicated to the quality assessment of the local data. Model-based results were compared across countries. Lifetime incremental cost-effectiveness ratios per QALY gained varied across countries: €4,525 (UK), €7,506 (Germany), €12,749 (Hungary), €-11,242 (healthcare perspective) and €-16,362 (societal perspective) for Sweden. Despite variation, advanced imaging, followed by late MT, is cost-effective in the 4 countries. Transferring the original model based on a 4-step approach appeared to be an efficient method to provide a preliminary assessment of the cost-effectiveness of late MT in different countries. We showed high validity of the cost-effectiveness estimates for Sweden. Moderate validity was shown for Germany and Hungary, with the quality of the local data being the main validity-limiting factor.

Chapter 7 presents the findings of our European web-based survey regarding the diagnostic and treatment strategies in patients with known or suspected ACS, as reported by respondents. The survey focused on ACS imaging and revascularisation treatments and on a range of clinical scenarios. Given the limited number of respondents, we clustered the responses for Sweden (20), the UK (16), Northern/Western Europe (17), Southern Europe (9), and Central Europe (7). Considerable variations between geographical areas were observed in terms of reported diagnostic modalities and treatment strategies. The differences reported may indicate that some patients do not receive the best available care and may experience different health outcomes across geographical areas. Larger studies and real-world data are needed to verify these observations and investigate their causes.

Patients with NOCAD are at a higher risk of cardiovascular events than patients with normal coronary arteries and may benefit from statin therapy. **Chapter 8** presented the potential cost-effectiveness of SPCCT (versus coronary CT angiography (CCTA)) in diagnosing and selecting patients with NOCAD for statin treatment in the UK, based on the identification of vulnerable coronary plaques. A de novo decision tree and a Markov trace were developed to model the expected outcomes for a hypothetical UK cohort of 50-year-old male patients with stable chest pain and no history of CAD. Our deterministic and probabilistic results showed that an imaging test providing increased sensitivity in detecting vulnerable plaques would add value compared to CCTA. Nevertheless, accurate data regarding the efficacy and adverse events of statin treatment are needed before the cost-effectiveness of SPCCT can be estimated more precisely in this population.

Discussion

In **Chapter 9,** an overview of the main findings of the studies is presented together with the implications of our results, the challenges encountered and the limitations of our approach. In light of our research questions, our findings are fourfold. First, despite limited data, there is a clear indication of considerable variation between European countries regarding the diagnostic workup and therapeutic interventions for patients suspected with stroke and patient presenting with ACS. Second, SPCCT is cost-effective in patients with ischaemic stroke in the UK and in the USA. A reduced specificity of SPCCT reduced its cost-effectiveness. Third, despite variation in country-specific cost-effectiveness estimates, advanced imaging, followed by late MT, appeared to be good value for money in Germany, Hungary and Sweden. However, based on a 4-step approach, we showed a suboptimal validity of our German and Hungarian cost-effectiveness estimates derived from the transfer of a cost-effectiveness model. Fourth, SPCCT is cost-effective in pa-

tients with NOCAD in the UK, provided increased sensitivity compared to competing technologies.

Our results have implications for test-developers, clinicians, policy makers and payers, and beyond, for scientific purposes. The definition of current care, the lack of data, the necessity to deal with uncertainty and the specific complexity of assessing diagnostics were the main challenges that we faced throughout our work. We highlighted the limitations of the narrow approach of cost-effectiveness analyses. Those limitations could be overcome by complementary methods such as mini-HTA, multi-criteria decision analysis (MCDA) and budget impact analyses. In order to confirm our cost-effectiveness estimates, further research is needed to collect real-world data, assess the clinical efficacy of SPCCT, address structural uncertainty, investigate the optimal deployment of advanced imaging in clinical practice and determine its maximum price.

General conclusion

Despite a lack of data and considerable practice variation across countries, we have used modelling techniques to assess the cost-effectiveness of complex diagnostic strategies in cardiovascular diseases. More specifically, we estimated the country-specific cost-effectiveness of the currently developed SPCCT modality in stroke and NOCAD care and identified the technical drivers of the value per disease area. We explained the relevance of our early HTA findings to the manufacturer and highlighted the necessity to sharpen our cost-effectiveness estimates once more evidence and (quality) data become available. The evidence of value of SPCCT might be required by decision makers or payers at a later time. Although CEAs form a solid pillar in value assessment regardless of the level of decision-making, they present limitations that complementary methods incorporating different stakeholder perspectives may overcome. Depending on the stage of diffusion and implementation of SPCCT, later in its life cycle, a more comprehensive approach including mini-HTA, MCDA and budget impact analyses might become relevant. In the current phase, our economic analyses present strong and useful evidence of how SPCCT is expected to be a promising diagnostic technology in cardiovascular diseases.

SAMENVATTING

Wereldwijd, in de context van introductie van medische technologie en stijgende kosten van de gezondheidszorg, is er een sterke behoefte aan wetenschappelijk bewijs om besluitvorming te ondersteunen betreffende het gebruik en de financiering van nieuwe technologieën. Health technology assessment (HTA) is de systematische evaluatie van de directe en bedoelde effecten van een technologie, als mede de indirecte en onbedoelde consequenties. Economische evaluaties zijn de kern van HTA en geven inzicht in de kosten en de effecten van een nieuwe technologie in vergelijking met een alternatief, in veel gevallen de huidige zorg. De onderzoeksmethoden kosteneffectiviteitsanalyse en kostenutiliteitsanalyse worden veel gebruikt en deze leiden vaak tot de generieke uitkomst van de kosten per voor kwaliteit gecorrigeerd levensjaar (Quality Adjusted Life Year, QALY). Een cruciale stap van een kosteneffectiviteitsanalyse of kostenutiliteitsanalyse is het vaststellen van de uitgangspunten, en dit betreft het definieren van de patiëntenpopulatie, de interventie, het vergelijkingsalternatief (comparator) en het perspectief van analyse. Het definieren van dergelijke uitgangspunten is ook noodzakelijk in het geval wetenschappelijke data uit verschillende bronnen mathematisch in een besliskundig model worden samengevoegd. Het belangrijkste doel van besliskundig modelleren in de context van de gezondheidzorg is om wetenschappelijk bewijs ten behoeve van besluitvorming te leveren, waarbij onzekerheid centraal staat. Onzekerheid in relatie tot besliskundige modellen bestaat uit drie onderdelen: onzekerheid betreffende de specifiek waarden van rekenparameters in het mathematisch model, verscheidenheid (heterogeniteit) in patiëntenpopulaties en ten derde de keuzen die ten grondslag liggen aan het model, zoals klinische gebeurtenissen en de gebruikte statistische methoden. Door deze concepten van onzekerheid expliciet te maken kan vroege-HTA tijdens de onderzoek- en ontwikkelingsfasen van een nieuwe technologie gebruikt worden om de fabrikant en andere belanghebbenden te informeren over de potentiele waarde van de technologie. Dit is vooral relevant voor diagnostische technologie omdat besliskundig modelleren tijdens de ontwikkelingsfase ontwikkelaars kan stimuleren technische mogelijkheden aan te passen om zodoende de waarde van de diagnostische technologie voor behandelbeslissingen, patiënten, zorgprofessionals, producenten, en de samenleving als geheel te verbeteren. Een positieve waardering kan dan leiden tot positieve beslissingen betreffende aankoop en/of vergoeding door zorgaanbieders en zorgautoriteiten. Ten slotte, omdat de waarde van een gezondheidstechnologie erg afhankelijk is van het gezondheidszorgsysteem waar deze ingezet gaat worden, is de aanpassing van gezondheidseconomisch bewijs van het ene naar het andere land mogelijk een snelle en efficiente methode om belanghebbenden in verschillende landen te informeren.

Aandoeningen

Cardiovasculaire ziekten (cardiovascular diseases, CVD) ofwel hart- en vaatziekten zijn de belangrijkste doodsoorzaken en gaan gepaard met wereldwijd aanzienlijke menselijke en economische consequenties. Deze ziekten betreffen aandoeningen van het hart en de bloedvaten, waaronder aandoeningen aan de kransslagaders, ofwel coronaire hartziekten en aandoeningen aan de bloedvaten in en naar de hersenen, ofwel cerebrovasculaire ziekten. Het merendeel van de CVD-gevallen wordt veroorzaakt door atherosclerose waarbij vet- of andere lichaamscellen zich ophopen in de binnenwand van de slagader en daar een plaque vormen. De plaque zelf en ook het scheuren of eroderen van de plaque kan leiden tot afsluiting van een bloedvat en zodoende cardiovasculaire incidenten veroorzaken zoals acuut coronair syndroom (waaronder myocardinfact ofwel hartaanval), ischemisch cerebrovasculair accident (ofwel beroerte) en/of overlijden. De nieuwe en innovatieve beeldvormende technologie, genaamd spectral photon counting computed tomography (SPCCT), heeft de potentie van waarde te zijn in het diagnostische traject van patiënten die een cardiovasculair incident doormaken of daar risico op lopen.

Dit proefschrift richt zich op twee belangrijke cardiovasculaire aandoeningen: ischemisch cerebrovasculair accident (ICVA) en de coronaire vaataandoeningen acuut coronair syndroom (ACS) en non-obstructief coronaire vaataandoeningen (non-obstructive coronary artery disease, NOCAD). Ten eerste richten we ons op acute patiënten met CVA-achtige symptomen. Deze moeten zo snel mogelijk onderzocht worden om de oorzaak en de kenmerken te bepalen van mogelijke hersenschade voordat de arts kan beslissen welke behandeling het beste is. SPCCT zal naar verwachting de besluitvorming in deze situatie verbeteren doordat de doorbloeding van de hersenen beter kan worden gequantificeerd. Daarnaast concentreert dit proefschrift zich op patiënten met pijn of druk op de borst. Hier moet de oorzaak van deze klachten worden vastgesteld voordat een behandeling kan worden bepaald. Door de hogere gevoeligheid van SPCCT voor calcificaties en betere beeldkwaliteit door een hoger aantal pixels kan worden verwacht dat de nauwkeurigheid van de meting van vernauwing van kransslagaders toeneemt. Daarnaast kan SPCCT de structuur en samenstelling van eventuele plaque beter vaststellen. Hierdoor kan SPCCT plaques identificeren die risico lopen te scheuren en zodoende kan besloten worden tot preventieve behandeling bij CAD.

Dit proefschrift

Het doel van dit proefschrift is om de potentiele kosteneffectiviteit van de in ontwikkeling zijnde diagnostische beeldvormende technologie SPCCT vast te stellen en hiermee gezondheidszorgbeslissingen te informeren, rekening houdend met internationale variatie. Vier onderzoeksvragen worden behandeld. 1) Wat is er bekend over de huidige

zorg en de variatie tussen vier Europese landen betreffende het diagnostisch traject en behandelbeleid voor patiënten verdacht een van cerebrovasculair accident, dan wel patiënten met klachten die wijzen op ACS? 2) Wat is de kosteneffectiviteit van SPCCT bij patiënten met ICVA in het Verenigd Koninkrijk (UK) en in de Verenigde Staten van America (USA)? 3) Is er internationale variatie in de kosteneffectiviteit van SPCCT bij patiënten met ICVA en is het valide om een economisch rekenmodel aan te passen om te komen tot land-specifieke schattingen? 4) Wat is de kosteneffectiviteit van SPCCT bij patiënten met NOCAD in de UK?

De studies

In **hoofdstuk 2** wordt een beschrijving gegeven van de momenteel bij cerebrovasculair accident (CVA) toegepaste beeldvormende technologieën en de variatie in de CVA-zorg tussen Duitsland, Hongarije, Zweden en de UK. Deze bevindingen zijn nodig om de huidige zorgpraktijk in onze kosteneffectiviteitsanalyses weer te geven. In een systematisch literatuuronderzoek werden originele onderzoeksstudies opgenomen waarin de diagnostische trajecten werden gepresenteerd in de zorg voor patiënten met CVA. Gebaseerd op een gericht ontwikkelde zoekstrategie werden vijf literatuur databases doorzocht en op basis hiervan werden 15 originele studies in het literatuuroverzicht opgenomen. De meeste van deze studies betroffen observationele studies op basis van nationale registers. Voor Hongarije werd geen enkele studie gevonden. Computed tomografie (CT) werd gerapporteerd als de belangrijkste beeldvormende technologie bij de zorg voor CVA-patiënten. Eenduidig bewijs van het optimale diagnostische traject voor deze patiënten ontbreekt. Verder bleek dat er onvoldoende bewijs is om een nauwkeurige vergelijking tussen de vier landen te maken betreffende dit diagnostisch traject.

Er is een veelheid van beeldvormende technologieën en behandelopties voor CVA. Om de bevindingen zoals gepresenteerd in hoofdstuk 2 aan te vullen en de huidige zorgpraktijk te bestuderen werd een online enquête ontwikkeld en verstuurd naar clinici in Europa. Ondanks een lage response rapporteren we in **hoofdstuk 3** de antwoorden uit Zweden (21), de UK (16), Hongarije (15), Duitsland (12) en overige Europese landen (47). De variatie tussen Europese landen met betrekking tot diagnostiek van acute CVA bleek beperkt wat betreft de eerst toegepaste beeldvormende technologie: CT werd gebruikt in 81% tot 93% van de patiënten. Echter, praktijkvariatie nam toe in de latere stadia van het beeldvormende diagnostische traject en in de keuze van de behandeling. Duitse en Britse respondenten rapporteerden dat respectievelijk 81% en 12% van de patiënten waarbij binnen 4,5 uur na aanvang van symptomen een grote arteriele vernauwing werd gediagnostiseerd, behandeld werd met intraveneuze bloedverdunning (trombolyse) en verwijdering van het bloedstolsel (trombectomie). Betreffende patiënten die binnen 2 uur gediagnostiseerd werden met een uitgebreid herseninfarct rapporteerde 75%

van de Britse respondenten dat zij trombectomie als behandeling prefereerden, maar tegelijkertijd deed slechts 13% dit daadwerkelijk. We concluderen dat nader onderzoek nodig is om de kwaliteit van CVA-zorg tussen landen te kunnen vergelijken en om te bepalen welke 2e-lijns beeldvormende technologie het meest kosteneffectief is om CVA-patiënten te diagnostiseren.

In **hoofdstuk 4** vergelijken we de kosteneffectiviteit van twee zorgpaden voor acute ICVA-patiënten in de UK: mechanisme trombectomie (MT) tot 6 uur na aanvang van symptomen op basis van conventionele beeldvorming versus MT tot, maar ook na 6 uur na aanvang van symptomen op basis van geavanceerde beeldvorming. Hiertoe ontwikkelden wij een beslisboom (die het korte termijn diagnostische en behandeltraject weergaf) en een Markov-model (die de lange termijn voortgang na CVA weergaf, tot overlijden) en we modelleerden hiermee de voortgang van een hypothetisch UK-cohort van 71-jarige patiënten. Verschillende scenario's gebaseerd op verschillende waarden van zowel de a priori-kans om baat te hebben van late MT als de accuraatheid van geavanceerde beeldvorming werden doorgerekend. Daarnaast werden probabilistische gevoeligheidsanalyses uitgevoerd. Incrementele kosteneffectiviteitsratio's (IKER) varieerden van $8.199 (£6.164) tot $49.515 (£37.229) per gewonnen QALY. Onze analyses lieten zien dat de accuraatheid van geavanceerde beeldvorming vooral invloed heeft op de incrementele kosteneffectiviteitsratio wanneer de specificiteit verlaagd wordt. Bij een levenslange tijdhorizon resulteerde late MT in alle scenario's tot gezondheidswinst (meer QALY's). Afhankelijk van het scenario lieten de probabilistische gevoeligheidsanalyses zien dat de kans dat het late MT-traject kosteneffectief was bij een kosteneffectiviteitsdrempelwaarde van $39.000 (£30.000) per gewonnen QALY varieerde tussen 46% en 93%. We lieten zien dat, in principe, late MT tot 12 uur na aanvang van symptomen een goede investering kan zijn. Echter, additionele gegevens zijn nodig betreffende de implementatie van geavanceerde beeldvorming en de a priori-kans van ICVA-patiënten om baat te hebben van late MT voor de kosteneffectiviteit kan worden vastgesteld.

Twee recente klinische trials (DAWN en DEFUSE 3) lieten zien dat er 3 maanden na behandeling positieve functionele effecten waren van late MT, tot 24 uur na aanvang van symptomen. Behandeling door middel van MT in het late tijdsbestek na aanvang van symptomen (tussen 6 en 24 uur) vereist selectie van patiënten op basis van geavanceerde beeldvorming. In **hoofdstuk 5** presenteren we hoe de korte termijn functionele effecten van late MT op basis van geavanceerde beeldvorming en standaard medische zorg (SMZ) zich lieten vertalen in kosteneffectiviteit in vergelijking met louter SMZ in de USA, uitgaande van een levenslange tijdshorizon. Op basis van een Amerikaans gezondheidszorg perspectief, werd een kosteneffectiviteitsmodel ontwikkeld, gebaseerd op de combinatie van een beslisboom en een Markov model en dit model werd ingevuld met

de bevindingen uit de DAWN en DEFUSE 3 studies. Voor de studiepopulaties waren de IKERs respectievelijk $662/QALY en $13.877/QALY. Late MT+SMZ (versus louter SMZ) had een kans van 99,9% om kosteneffectief te zijn bij een kosteneffectiviteitsdrempel van $100.000/QALY. Subgroep analyses lieten zien dat bij een kosteneffectiviteitsdrempelwaarde van $50.000/QALY deze kans een breed bereik kende, waarbij de belangrijkste onzekerheid gold voor patiënten met een NIHSS-score ≥ 16 (National Institutes of Health Stroke Scale) en patiënten van 80 jaar en ouder.

In **hoofdstuk 6** wordt de internationale variatie betreffende de waarde van SPCCT voor ICVA-patiënten gepresenteerd, als ook een methode om te beoordelen wat de validiteit is van het transfereren van kosteneffectiviteitsbevindingen van het ene naar het andere land. Een vier-stappen benadering werd ontwikkeld die de principes van McCabe en Welte combineerde en deze werd toegepast om de validiteit van het transfereren van het model zoals gepresenteerd in hoofdstuk 4 van de UK naar Duitsland, Hongarije en Zweden te bepalen. Het UK-model bleek passend voor de beslissingscontext van deze drie landen. Beperkende factoren voor het transfereren van de UK-bevindigen werden vastgesteld en hiervoor werden steeds lokale gegevens verkregen. Ook werd van deze gegevens de kwaliteit bepaald. De resultaten gebaseerd op de kosteneffectiviteitsmodellen van de landen werden met elkaar vergeleken en hierbij bleek er variatie in de resultaten wat betreft de incrementele kosteneffectiviteit in gewonnen QALY op basis van een levenslange tijdhorizon: €4.525 (UK), €7.506 (Duitsland), €12.749 (Hongarije) en voor Zweden gebaseerd op een gezondheidsperspectief en een maatschappelijke perspectief, respectievelijk -€11.242 en -€16.362. Ondanks deze variatie bleek geavanceerde beeldvorming gevolgd door late MT kosteneffectief in de vier landen. Transfereren van het originele model door middel van de vier-stappen benadering bleek een efficiënte methode om een voorlopige analyse van de kosteneffectiviteit van late MT in verschillende landen uit te voeren. We lieten zien dat er een hoge validiteit is van de kosteneffectiviteitsuitkomsten voor Zweden. Een beperkte betrouwbaarheid bleek het geval te zijn voor Duitsland en Hongarije, waarbij de kwaliteit van lokale gegevens de beperkende factor was.

In **hoofdstuk 7** worden de resultaten gepresenteerd van een online enquête betreffende de diagnostische- en behandelstrategieën van patiënten bekend met of verdacht van ACS, zoals gerapporteerd door patiënten. De vragenlijst richtte zich op beeldvorming en behandelingen voor revascularisatie en daarnaast ook op enkele klinische scenario's. Gegeven het beperkte aantal respondenten werden de antwoorden gegroepeerd van Zweden (20), de UK (16), Noord-/West-Europa (17), Zuid-Europa (9) en Centraal-Europa (7). Aanzienlijke variatie werd gevonden tussen de verschillende geografische gebieden betreffende diagnostische trajecten en behandelstrategieen. De gerapporteerde

verschillen gaven mogelijk aan dat sommige patiënten niet de best gangbare zorg ontvingen en dat er gezondheidsverschillen waren tussen gebieden. Grotere studies en data uit de dagelijkse zorgpraktijk zijn noodzakelijk om onze bevindingen te verifiëren en achterliggende oorzaken aan het licht te brengen.

NOCAD-patiënten hebben een hoger risico op cardiovasculaire incidenten dan patiënten met normale kransslagaders waardoor zij mogelijk baat hebben bij behandeling met statines. **Hoofdstuk 8** presenteert de potientiele kosteneffectiviteit van SPCCT (versus coronair CT angiografie, CCTA) in de diagnostiek en selectie van NOCAD-patiënten voor statinebehandeling in de UK, gebaseerd op de aanwezigheid en samenstelling van arteriele plaque. Een beslisboom en Markov model werden ontwikkeld om hiermee de verwachte uitkomsten voor een hypothetisch cohort van 50-jarige mannelijk patiënten met stabiele angina pectoris (pijn op de borst), zonder voorgaande CAD. Onze deterministische en probabilistische resultaten lieten zien dat beeldvorming met een hogere sensitiviteit om instabiele plaques te detecteren van waarde is ten opzichte van CCTA. Desalniettemin zijn preciese gegevens nodig inzake de werkzaamheid en bijwerkingen van statinebehandeling voordat de kosteneffectiviteit van SPCCT bij deze populatie nauwkeurig kan worden vastgesteld.

Discussie

In **hoofdstuk 9** wordt het overzicht van de belangrijkste bevindingen van de studies gegeven met daarbij de implicaties van onze resultaten, de uitdagingen die we zijn tegengekomen en de beperkingen van onze aanpak. Gegeven onze onderzoeksvragen kunnen we de bevindingen in vier punten samenvatten. Ten eerste kan, ongeacht de beperkte gegevens, worden gesteld dat er een duidelijke aanwijzing is voor aanzienlijke variatie tussen Europese landen wat betreft het diagnostisch traject en behandelbeleid voor patiënten verdacht van een cerebrovasculair accident en patiënten met klachten die wijzen op ACS. Ten tweede blijkt dat SPCCT kosteneffectief is bij patiënten met ICVA in de UK en de USA. Een lagere specificiteit van SPCCT (de kans op een negatieve testuitslag bij personen zonder de aandoening) vermindert de kosteneffectiviteit. Ten derde werd aangetoond dat ondanks variatie in de kosteneffectiviteit tussen landen geavanceerde beeldvorming gevolgd door late MT de investering waard is in Duitsland, Hongarije en Zweden. Echter, middels de vier-stappen benadering laten we zien dat het transferen van een kosteneffectiviteitsmodel naar Duitsland en Hongarije leidt tot beperkte validiteit van resultaten. Ten vierde stellen we vast dat SPCCT bij patiënten met NOCAD in de UK kosteneffectief is zolang de sensitiviteit (de kans op een positieve testuitslag bij personen met de aandoening) hoger is dan bij andere beeldvormende technologieën.

Onze resultaten hebben implicaties voor de ontwikkelaars van diagnostische tests, zorgverleners, beleidsmakers, financiers en verzekeraars en bovendien de wetenschap. De definitie van huidige zorg, de schaarste aan gegevens, de noodzaak om rekening te houden met onzekerheid en de specifieke complexiteit van de evaluatie van diagnostisch technologie waren de belangrijkste uitdagingen die we in de totstandkoming van dit proefschrift tegenkwamen. We hebben de beperkingen van de gerichte benadering van kosteneffectiviteitsanalyses laten zien. Dergelijke beperkingen kunnen worden gepareerd door toepassing van complementaire onderzoeksmethoden zoals mini-HTA, multi-criteria beslissingsanalyse (MCDA) en budget impact analyses. Om onze kosteneffectiviteitsschattingen te bevestigen is verder onderzoek noodzakelijk naar gegevens uit de dagelijkse zorgpraktijk, als ook het vaststellen van de klinische werkzaamheid van SPCCT, de structurele onzekerheid van onze modellen, en bovenal het onderzoeken van de optimale toepassing van geavanceerde beeldvorming in de zorgpraktijk en het vaststellen van de maximaal acceptabele prijs.

Algemene conclusie

Ongeacht de schaarste aan gegevens en aanzienlijke zorgpraktijkvariatie tussen landen hebben we modelleringsmethoden toegepast om de kosteneffectiviteit van complexe diagnostische strategieen bij cardiovasculaire aandoeningen te schatten. Hiermee hebben we de landspecifieke kosteneffectiviteit van de in ontwikkeling zijnde technologie SPCCT berekend ten behoeve van zorg voor patiënten met CVA en NOCAD en hierbij hebben we per aandoening de technische kenmerken vastgesteld die deze waarde in grote mate bepalen. Hiermee laten we de relevantie van onze vroege HTA-bevindingen aan mogelijke fabrikanten zien en geven de noodzaak aan de kosteneffectiviteitsbevindingen te actualiseren in het geval er betere gegevens beschikbaar komen. In een later stadium wordt wellicht dergelijk bewijs over de waarde van SPCCT vereist door beleidsmakers of financiers. Alhoewel kosteneffectiviteitsanalyses ongeacht de beslissingscontext een belangrijke basis vormen voor de waardebepaling van een technologie, hebben deze beperkingen die door complementaire onderzoeksmethoden vanuit het perspectief van diverse belanghebbenden kunnen worden gecompenseerd. Afhankelijk van de mate van toepassing en implementatie gerelateerd aan de levenscyclus van SPCCT kan een bredere benadering, waaronder mini-HTA, MCDA en budget impact analyses, relevant worden. In de huidige fase van de levenscyclus van SPCCT geven onze economische analyses desalniettemin sterk en nuttig bewijs van hoe SPCCT een veelbelovende diagnostische technologie kan zijn bij cardiovasculaire aandoeningen.

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PHD PORTFOLIO

PhD training

Academic writing in English, Erasmus University Rotterdam, Rotterdam, The Netherlands, 2016.

Professionalism and integrity in research, Erasmus University Rotterdam, Rotterdam, The Netherlands, 2017.

Cross-cultural awareness and communication, Erasmus University Rotterdam, Rotterdam, The Netherlands, 2017.

Advanced decision analytic modelling for economic evaluation, University of Glasgow, Scotland, 2017.

Collecting health-state utility estimates for economic models in clinical studies, short course, International Society for Pharmacoeconomics and Outcomes Research (ISPOR) 20th Annual European Congress, Glasgow, Scotland, 2017.

Introduction to R, Decision Analysis in R for Technologies in Health (DARTH group), Leiden, The Netherlands, 2018.

Decision modelling using R, Decision Analysis in R for Technologies in Health (DARTH group), Leiden, The Netherlands, 2018.

Budget impact analysis I and II, short course, International Society for Pharmacoeconomics and Outcomes Research (ISPOR) 21st Annual European Congress, Barcelona, Spain, 2018.

Introduction to Infectious Disease Modelling and its Applications, London School of Hygiene & Tropical Medicine, online, 2020.

Communicating your research: lessons from Bitescience, Erasmus University Rotterdam, Rotterdam, The Netherlands, 2020.

Self-presentation: focus, structure, interaction and visualisation, Erasmus University Rotterdam, Rotterdam, The Netherlands, 2020.

Teaching

Supervision of 1 thesis, master program Health Economics, Policy and Law, Erasmus School of Health Policy and Management, Erasmus University Rotterdam, Rotterdam, The Netherlands, 2019.

(Co-)supervision of 1 thesis, research master program Health Sciences NIHES, Erasmus Medical Center Rotterdam, Rotterdam, The Netherlands, 2018-2019.

Supervision of 6 theses, European Master in Health Economics and Management, Erasmus School of Health Policy and Management, Erasmus University Rotterdam, Rotterdam, The Netherlands, 2018-2020.

Co-evaluation of 1 thesis, master program Health Economics, Policy and Law, Erasmus School of Health Policy and Management, Erasmus University Rotterdam, Rotterdam, The Netherlands, 2020.

Pharmaceutical pricing and market access, master program Health Economics, Policy and Law, Erasmus School of Health Policy and Management, Erasmus University Rotterdam, Rotterdam, The Netherlands, 2016-2020.

Advanced health economic modelling, master program Health Economics, Policy and Law, Erasmus School of Health Policy and Management, Erasmus University Rotterdam, Rotterdam, The Netherlands, 2018.

Health economics, summer course NIHES, Erasmus Medical Center Rotterdam, Rotterdam, The Netherlands, 2017-2019.

Podium presentations

Spectral photon counting computed tomography, SPCCT semi-annual meeting, Cliniques Universitaires Saint-Luc, Brussels, Belgium, 14-15 December 2016.

Spectral photon counting computed tomography, SPCCT semi-annual meeting, Erasmus School of Health Policy and Management, Erasmus University Rotterdam, Rotterdam, The Netherlands, 22-23 June 2017.

Role and contribution of health technology assessment (HTA) in positioning imaging innovation; 2nd Spectral CT Workshop, Lyon, France, 17 November 2017.

Spectral photon counting computed tomography, SPCCT semi-annual meeting, St. Thomas Hospital, London, United Kingdom, 4-5 December 2018.

Spectral photon counting computed tomography, SPCCT semi-annual meeting, Molecular Biotechnology Center MBC – University of Turin, Turin, Italy, 3-4 July 2018.

Spectral photon counting computed tomography, SPCCT semi-annual meeting, Philips site, Hamburg, Germany, 20 September 2019.

Exploring the window of opportunity: Cost-effectiveness of mechanical thrombectomy beyond six hours following advanced imaging (versus thrombectomy within six hours following CT-CTA) in acute ischemic stroke in the UK. The 11th lowlands Health Economic Study Group (lolaHESG), Almen, The Netherlands, 23-24 May 2019.

Validity and comparison of transferred cost-effectiveness results across 4 countries: the case of advanced imaging + late thrombectomy in stroke care. The 12th lowlands Health Economic Study Group (lolaHESG), online, 24 September 2020.

Poster presentations

What are the images used to diagnose and assess suspected strokes?: A systematic literature review of care in four European countries. International Society for Pharmacoeconomics and Outcomes Research (ISPOR) 20th Annual European Congress, Glasgow, Scotland. Research poster presentation, 4-8 November 2017.

What stroke image do we want? European clinician survey on acute stroke imaging and revascularisation treatment. International Society for Pharmacoeconomics and Outcomes Research (ISPOR) 20th Annual European Congress, Glasgow, Scotland. Research poster presentation, 4-8 November 2017.

Potential cost-effectiveness of spectral photon-counting computed tomography (SPCCT) versus CT combined to CT angiography (CTA) in the identification and treatment of ischaemic stroke patients in the UK. International Society for Pharmacoeconomics and Outcomes Research (ISPOR) 21st Annual European Congress, Barcelona, Spain. Research poster presentation, 10-14 November 2018.

Exploring the daily clinical practice in myocardial infarction (MI) care in Europe: survey of diagnostic and treatment strategies for theoretical patients. International Society for Pharmacoeconomics and Outcomes Research (ISPOR) 21st Annual European Congress, Barcelona, Spain. Research poster presentation, 10-14 November 2018.

Transferability of UK-based cost-effectiveness model to Hungary, Sweden, and Germany: the case of mechanical thrombectomy beyond six hours following advanced-imaging (versus mechanical thrombectomy within six hours following CT+CTA) in acute ischaemic stroke. International Society for Pharmacoeconomics and Outcomes Research (ISPOR) 22nd Annual European Congress, Copenhagen, Denmark, 2-6 November 2019.

Preliminary budget impact analysis of advanced imaging and mechanical thrombectomy for acute ischaemic stroke beyond 6 hours from onset in the United Kingdom. International Society for Pharmacoeconomics and Outcomes Research (ISPOR) 23rd Annual European Congress, virtual, 16-19 November 2020.

Cost-effectiveness of imaging strategies to diagnose and select patients with non-obstructive coronary artery disease for statin treatment in the United Kingdom.
European Association of Cardiovascular Imaging (EACVI) - Best of Imaging 2020, virtual, 11-12 December 2020.

Co-authored poster presentations

Access to intravenous tissue-like plasminogen activator (IV TPA) therapy and mechanical thrombectomy (MT) for patients with acute ischemic stroke in Hungary. International Society for Pharmacoeconomics and Outcomes Research (ISPOR) 22nd Annual European Congress, Copenhagen, Denmark, 2-6 November 2019.

Beyond Acute Neisseria gonorrhoea infection: a model-based analysis estimating the holistic humanistic burden in England and the USA. International Society for Pharmacoeconomics and Outcomes Research (ISPOR) 23rd Annual European Congress, virtual, 16-19 November 2020.

Co-authored podium presentation

A model-based estimation of the cost-of-illness associated with Neisseria gonorrhoea in England and the USA: assessing the potential impact of antimicrobial resistance and long-term health problems. International Society for Pharmacoeconomics and Outcomes Research (ISPOR) 23rd Annual European Congress, virtual, 16-19 November 2020.

LIST OF PUBLICATIONS

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ABOUT THE AUTHOR

Anne-Claire Marie Monique Peultier was born in Nancy, France in 1985. After her bachelor's degree in Economics and Social Sciences, she obtained a master's degree in Management in 2008 (Institut Mines-Télécom Business School, Évry, France). During her master's, she studied one semester in Germany (Pforzheim University) and one year in Mexico (MBA program, Monterrey Institute of Technology).

Anne-Claire started her career in 2006 as an intern in marketing within the global team in Alcatel-Lucent France. From 2008 to 2010, she worked within the regional team in the United States of America and within the local team in Mexico. Subsequently, she joined Amadeus, where she carried out project management and product management responsibilities in France until 2016.

In 2015, she obtained a master's degree in Health Economics, Policy and Management (Erasmus University Rotterdam). In 2016, she joined the Health Technology Assessment section of the Erasmus School of Health Policy and Management (Erasmus University Rotterdam) as a PhD candidate. Her core research focused on health-economic modelling of a new diagnostic imaging technique.

Alongside her doctoral research, Anne-Claire was involved in projects focusing on infectious diseases such as field work in Cameroon for a micro-costing study and supervision of various master thesis students in collaboration with the pharmaceutical industry.